

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Lupkynis 7.9 mg soft capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each soft capsule contains 7.9 mg of voclosporin.

### Excipients with known effect

Each soft capsule contains 21.6 mg ethanol and 28.7 mg sorbitol.  
Lupkynis may contain trace amounts of soya lecithin, see section 4.4.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Soft capsule (capsule)  
Pink/orange oval soft capsules measuring approximately 13 mm × 6 mm.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Lupkynis is indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN).

### **4.2 Posology and method of administration**

Lupkynis treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of lupus nephritis.

#### Posology

The recommended dose is 23.7 mg (three 7.9 mg soft capsules), twice daily.

It is recommended that Lupkynis is administered consistently as close to a 12-hour schedule as possible and with a minimum of 8 hours between each dose. If a dose is missed, it should be taken as soon as possible within 4 hours after missing the dose; beyond the 4-hour time frame, the next regular dose should be taken at the usual scheduled time. The next dose should not be doubled.

Lupkynis should be used in combination with mycophenolate mofetil.

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 with voclosporin, and assess every two weeks for the first month, and every four weeks

thereafter.

Dose adjustments are required for those individuals whose eGFR is confirmed to be reduced (i.e., two consecutive assessments within 48 hours) and below 60 mL/min/1.73 m<sup>2</sup>. If eGFR remains  $\geq$  60 mL/min/1.73 m<sup>2</sup> no dose modification is required (see table 1).

**Table 1: Recommended dose adjustments based on eGFR**

<b>Confirmed eGFR decrease from baseline<sup>1</sup></b>	<b>Recommendation</b>
$\geq$ 30 % reduction	Stop administration of voclosporin. Restart treatment upon eGFR recovery at 7.9 mg (1 capsule) twice daily and increase as tolerated based on renal function.
> 20 % and < 30 % reduction	Reduce dose of voclosporin 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.
$\leq$ 20 % reduction	Maintain current dose and monitor.

<sup>1</sup> If eGFR remains  $\geq$  60 mL/min/1.73 m<sup>2</sup> no action is required

It is recommended that patients requiring a reduction in dose are reassessed for eGFR recovery within two weeks. For patients that had a decrease in dose due to eGFR reduction, increasing the dose by 7.9 mg twice a day for each eGFR measurement that is  $\geq$  80 % of baseline should be considered; the starting dose should not be exceeded.

#### *Co-administration with moderate CYP3A4 inhibitors*

When co-administering Lupkynis with moderate cytochrome P450 (CYP)3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem), daily dose must be reduced to 15.8 mg in the morning and 7.9 mg in the evening (see section 4.5).

#### *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 voclosporin in patients with severe hepatic impairment (Child-Pugh Class C) has not been assessed and voclosporin is not recommended in this patient population (see sections 4.4 and 5.2).

#### *Renal impairment*

Careful monitoring of renal function is recommended (see table 1 and section 4.4). Limited data are available on the use of Lupkynis in patients with baseline eGFR 30 to < 45 mL/min/1.73 m<sup>2</sup>. It is recommended to use Lupkynis in these patients, 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<sup>2</sup>) and is not recommended in these patients unless the benefit outweighs the risk. If used, the recommended starting dose is 15.8 mg twice daily (see section 5.2).

#### *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 (see section 5.2).

#### *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.

#### Method of administration

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 (see section 4.5).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration of voclosporin with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) (see section 4.5).

### **4.4 Special warnings and precautions for use**

#### Lymphomas and other malignancies

Immunosuppressants increase the risk of developing lymphomas and other malignancies, particularly of the skin. It is recommended that patients are advised to avoid or limit unprotected exposure to sunlight and UV light.

#### Serious infections

Immunosuppressants, including voclosporin, may increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections which may be serious or fatal (see section 4.8). Patients must be monitored closely for infections during treatment with voclosporin. If an infection occurs, the benefit of continuing voclosporin should be assessed in consideration of the risk of continued administration.

#### Renal toxicity

As with other calcineurin-inhibitors, adverse reactions of acute worsening of renal function or eGFR decreases have been seen in patients treated with voclosporin. In the first four weeks of treatment with voclosporin, haemodynamic reductions in eGFR have been observed (see section 4.8). This can be managed by dose adjustments. Regular monitoring of eGFR levels is recommended (see section 4.2).

#### Pure red cell aplasia

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. The mechanism of PRCA due to calcineurin inhibitors has not been clarified. If PRCA is diagnosed, discontinuation of Lupkynis should be considered.

#### Hyperkalaemia

Hyperkalaemia, which may be serious and require treatment, has been reported with calcineurin inhibitors, including voclosporin (see section 4.8). Concomitant use of medicinal products associated with hyperkalaemia (e.g., potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)) may increase the risk of hyperkalaemia. It is recommended that patients are monitored for serum potassium levels periodically during treatment.

#### Hypertension

Voclosporin can cause or worsen systemic hypertension (see section 4.8). Blood pressure should be monitored every two weeks for the first month after initiating voclosporin, and as clinically indicated thereafter. In the event of clinically concerning elevated blood pressure, the recommendations in table 2 should be followed.

**Table 2: Recommendations for management of hypertension**

<b>Blood pressure</b>	<b>Recommendation</b>
Systolic pressure > 130 and ≤ 165 mmHg and Diastolic pressure > 80 and ≤ 105 mmHg	Antihypertensive therapy may be initiated/adjusted
Blood pressure > 165/105 mmHg, with symptoms of hypertension	Stop administration of voclosporin and initiate/adjust antihypertensive therapy

#### QT prolongation

The use of voclosporin 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 voclosporin, are at increased risk of neurotoxicity (see section 4.8). Patients should be monitored for new-onset or worsening of neurological symptoms including seizures, tremors, or signs and symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) and reduction or discontinuation of voclosporin should be considered if these occur.

#### Hepatic impairment

Voclosporin has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population.

#### Vaccination

Immunosuppressants may affect the response to vaccination, and vaccination during treatment with voclosporin may be less effective. The use of live attenuated vaccines should be avoided.

#### Concomitant use with other medicinal products

Co-administration of voclosporin with moderate or strong CYP3A4 inducers is not recommended (see section 4.5).

The safety and efficacy of voclosporin have not been established in combination with cyclophosphamide.

#### Excipients

##### *Ethanol*

This medicinal product contains 21.6 mg of alcohol (ethanol) in each soft capsule. Therefore, a dose of 23.7 mg of Lupkynis contains 64.8 mg ethanol. The amount in each 23.7 mg dose of this medicinal product is equivalent to less than 2 mL beer or 1 mL wine. The small amount of alcohol in this medicinal product will not have any noticeable effects.

##### *Sorbitol*

This medicinal product contains 28.7 mg of sorbitol in each soft capsule. 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Voclosporin is metabolised by CYP3A4 and is an inhibitor of P-glycoprotein (P-gp) and organic-anion-transporting polypeptide (OATP)1B1 and OATP1B3.

##### Potential for other medicinal products to affect voclosporin exposure

Voclosporin is metabolised by CYP3A4. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of voclosporin and thereby increase or decrease voclosporin blood levels.

##### *CYP3A4 inhibitors*

Voclosporin exposure was 18.6-fold higher in the presence of the strong CYP3A4 inhibitor ketoconazole compared to voclosporin administered alone. Co-administration of voclosporin with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is contraindicated (see section 4.3).

Voclosporin exposure was 2.71-fold higher in the presence of the moderate CYP3A4 inhibitor verapamil compared to voclosporin administration alone. Reduce the dose to 15.8 mg in the morning and 7.9 mg in the evening when voclosporin is co-administered with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, erythromycin, diltiazem, grapefruit and grapefruit juice, see section 4.2).

Mild CYP3A4 inhibitors may increase voclosporin exposure, but no in vivo study has been performed. No dose adjustment is required when voclosporin is co-administered with mild CYP3A4 inhibitors but additional monitoring of eGFR is recommended when initiating treatment with a mild CYP3A4 inhibitor.

##### *CYP3A4 inducers*

Voclosporin exposure was 87 % lower and maximum concentration ( $C_{\max}$ ) was 68 % lower in the presence of the strong CYP3A4 inducer rifampicin (600 mg once daily for 10 consecutive days) compared to voclosporin administration alone. Co-administration of multiple doses of moderate CYP3A4 inducers are also expected to result in clinically relevant decreases of voclosporin exposure.

Strong and moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, rifampicin, St John's Wort, efavirenz) are not recommended to be dosed concomitantly with voclosporin (see section 4.4). Mild inducers of CYP3A4 may also result in decreased exposure and possibly a decreased effect, but the clinical relevance is unknown.

##### Potential for voclosporin to affect exposure to other medicinal products

##### *P-gp substrates*

Voclosporin is an inhibitor of P-glycoprotein (P-gp). Concomitant administration of voclosporin with multiple doses of digoxin increased digoxin  $C_{\max}$  and area under the curve (AUC) by 1.51-fold and 1.25-fold, respectively. Caution must be exercised in case of co-administration of voclosporin with sensitive P-gp substrates, especially those with narrow therapeutic index (e.g., digoxin, dabigatran etexilate, fexofenadine) where patients should be appropriately monitored as outlined in respective product labelling.

##### *OATP1B1/OATP1B3 substrates*

Voclosporin is an inhibitor of OATP1B1 and OATP1B3 transporters. In one clinical study the concomitant administration of a single 40 mg dose of simvastatin with 23.7 mg BID voclosporin increased  $C_{\max}$  and AUC of the active metabolite simvastatin acid (a sensitive OATP1B1/OATP1B3

substrate) by 3.1-fold and 1.8-fold, respectively. In the same study, exposure of the parent drug simvastatin (which is also a BCRP substrate) was unaffected in terms of AUC while its  $C_{max}$  increased by 1.6-fold, which could potentially be attributed to an interaction between intestinal BCRP and voclosporin. Patients should be monitored for adverse events such as myopathy and rhabdomyolysis when OATP1B1/OATP1B3 substrates (e.g., simvastatin, atorvastatin, pravastatin, rosuvastatin) are used concomitantly with voclosporin.

#### *BCRP substrates*

Voclosporin inhibits breast cancer resistance protein (BCRP) *in vitro*. A clinically relevant inhibition of intestinal BCRP cannot be excluded and voclosporin 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 voclosporin.

#### *MMF*

Co-administration of voclosporin with mycophenolate mofetil (MMF) had no clinically significant impact on mycophenolic acid (MPA) blood concentrations.

#### *CYP3A4 substrates*

Multiple administrations of voclosporin orally (0.4 mg/kg twice daily) had no clinically relevant effect on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of voclosporin in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3).

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 (see section 5.2). 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 taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### Fertility

There are no data on the effect of voclosporin on human fertility. In animal studies, voclosporin-related changes in the male reproductive tract were observed (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Lupkynis has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most frequently reported adverse reactions with use of voclosporin are decreased eGFR (26.2 %) and hypertension (19.1 %).

The most frequently reported serious adverse reactions with use of voclosporin were infections (10.1 %), acute kidney injury (3 %) and hypertension (1.9 %).

In the first 4 weeks of treatment with voclosporin, haemodynamic reductions in eGFR are commonly experienced, which subsequently stabilise, even if treatment is continued (see section 4.4).

#### Tabulated list of adverse reactions

Adverse reactions that occurred in patients with LN receiving the recommended dose of voclosporin with a median treatment duration of 1 year in two placebo-controlled clinical studies and/or post-marketing use are summarised in table 3.

All adverse reactions are listed by system organ class (SOC) and frequency: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**Table 3: Adverse reactions**

System organ class	Very common	Common	Not known
<b>Infections and infestations</b>	Upper respiratory tract infection <sup>1</sup>	Pneumonia Influenza Herpes zoster Gastroenteritis Urinary tract infection	
<b>Blood and lymphatic system disorders</b>	Anaemia		
<b>Immune system disorders</b>			Hypersensitivity
<b>Metabolism and nutrition disorders</b>		Hyperkalaemia Decreased appetite	
<b>Nervous system disorders</b>	Headache	Seizure Tremor	
<b>Vascular disorders</b>	Hypertension <sup>2</sup>		
<b>Respiratory, thoracic and mediastinal disorders</b>	Cough		
<b>Gastrointestinal disorders</b>	Diarrhoea Abdominal pain <sup>3</sup>	Nausea Gingival hyperplasia <sup>4</sup> Dyspepsia Mouth ulceration	
<b>Skin and subcutaneous tissue disorders</b>		Alopecia Hypertrichosis <sup>5</sup>	
<b>Renal and urinary disorders</b>	Glomerular filtration rate decreased <sup>6,7</sup>	Acute kidney disease <sup>6</sup> Acute kidney injury <sup>6</sup>	
<b>General disorders and administration site conditions</b>		Fatigue	

<sup>1</sup> Includes the following Preferred Terms (PTs): viral upper respiratory tract infection and upper respiratory tract infection bacterial

<sup>2</sup> Includes the following PTs: blood pressure increased, blood pressure diastolic increased, diastolic hypertension

<sup>3</sup> Includes the following PTs: abdominal pain upper, abdominal discomfort

<sup>4</sup> Includes the following PTs: gingivitis, gingival bleeding, gingival hypertrophy, gingival swelling

<sup>5</sup> Includes the following PTs: hypertrichosis, hirsutism

<sup>6</sup> Includes the PT renal impairment

<sup>7</sup> Includes the PT blood creatinine increased



## Description of selected adverse reactions

### *Infections*

The overall incidence of infections was 62.2 % in the voclosporin group and 54.9 % in the placebo group. Infections occurring in at least 5 % of patients receiving voclosporin and at least 1 % more frequently than patients receiving placebo were urinary tract infection, viral upper respiratory tract infection, herpes zoster and gastroenteritis. Serious infections occurred in 10.1 % of voclosporin and 10.2 % of placebo patients; the most common were pneumonia (voclosporin 4.1 %, placebo 3.8 %), gastroenteritis (voclosporin 1.5 %, placebo 0.4 %) and urinary tract infection (voclosporin 1.1 %, placebo 0.4 %). Serious opportunistic infections occurred in 1.1 % of voclosporin patients and 0.8 % of placebo patients. Fatal infections occurred in 0.7 % of patients receiving voclosporin and in 0.8 % of patients receiving placebo (see section 4.4).

### *Renal toxicity*

Adverse reactions suggestive of renal toxicity which occurred at a frequency of  $\geq 1$  % higher in voclosporin compared to placebo were decreased eGFR (26.2 % vs. 9.4 %), renal impairment (5.6 % vs. 2.6 %), acute kidney injury (3.4 % vs. 0.8 %), and hyperkalaemia (1.9 % vs. 0.8 %). Serious adverse reactions were reported in 5.2 % of voclosporin patients and 3.4 % of placebo patients. The most common adverse reactions leading to dose modification (reduction in dose or temporary discontinuation) were decreased eGFR (voclosporin 23.6 %, placebo 6.8 %), renal impairment (voclosporin 3.0 %, placebo 0.8 %) and acute kidney injury (voclosporin 0.7 %, placebo 0). The most common adverse reactions leading to permanent medicinal product discontinuation were eGFR decreases (voclosporin 3.7 %, placebo 1.9 %) and renal impairment (voclosporin 1.9 %, placebo 1.5 %). Following a decrease in eGFR, the median time to recovery was 49 days for patients on voclosporin with an eGFR decrease  $\geq 20$  %. Similarly for patients with an eGFR decrease of  $\geq 30$  %, the median time to recovery was 102 days on voclosporin.

### *Hypertension*

Hypertension was reported in 19.1 % of voclosporin patients and 8.6 % of placebo patients. The incidence of hypertension was highest in the first 4 weeks of treatment with voclosporin and declined thereafter. Hypertension was severe in 1.1 % of voclosporin patients and 0.8 % of placebo patients. Serious hypertension occurred in 1.9 % of voclosporin patients and 0.4 % of placebo patients.

## Long term exposure (up to 36 months)

The pattern of adverse reactions with continued treatment (from 12 to 36 months) was consistent with that seen in the first year of treatment; however, the incidences of the vast majority of events were lower in subsequent years. The overall incidence of infections was 49.1 % in the voclosporin group and 43.0% in the placebo group. Infections occurring in at least 5 % of patients receiving voclosporin and at least 1 % more frequently than patients receiving placebo were urinary tract infection, upper respiratory tract infection, viral upper respiratory tract infection and gastroenteritis. Serious infections occurred in 6.9 % of voclosporin and 8.0 % of placebo patients; the most common were corona virus infection (voclosporin 1.7 %, placebo 5.0 %) and pneumonia viral (voclosporin 1.7 %, placebo 0 %). Adverse reactions suggestive of renal toxicity which occurred at a higher frequency in voclosporin compared to placebo were decreased eGFR (10.3 % vs. 5.0 %) and renal impairment (3.4 % vs. 2.0 %). Hypertension was reported in 8.6 % of voclosporin patients and 7.0 % of placebo patients.

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

Cases of accidental overdose have been reported with voclosporin; symptoms included tremor and

tachycardia. In an interaction study in healthy volunteers, co-administration of ketoconazole and voclosporin resulted in an 18.6-fold increase in voclosporin exposure and increases in serum creatinine, decreases in serum magnesium and increases in blood pressure were observed. Symptoms of overdose with other calcineurin inhibitors (but not observed with voclosporin) 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 voclosporin therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted, including temporarily stopping treatment with voclosporin and assessing blood urea nitrogen, serum creatinine, eGFR and alanine aminotransferase levels.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors, ATC code: L04AD03

#### Mechanism of action

Voclosporin is a calcineurin-inhibitor immunosuppressant that inhibits calcineurin in a dose-dependent manner up to a maximum dose of 1.0 mg/kg. Activation of lymphocytes involves an increase in intracellular calcium concentrations. Calcineurin is a calcium/calmodulin-dependent phosphatase whose activity is required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.

#### Pharmacodynamic effects

##### *Cardiac electrophysiology*

In a randomised, placebo- and active-controlled (moxifloxacin 400 mg), single dose study with parallel study design, dose-dependent QT prolonging effect was detected with voclosporin in the dose range of 0.5 mg/kg to 4.5 mg/kg (up to 9-fold coverage of the therapeutic exposure). Dose-dependent QT prolongation effect was observed with a time to maximum QTc increase occurring at 4 hours to 6 hours post-dose across different dose levels. The maximum mean placebo-adjusted changes of QTcF from baseline after voclosporin 0.5 mg/kg, 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg dose were 6.4 msec, 17.5 msec, 25.7 msec, and 34.6 msec, respectively.

In a separate, randomised, placebo-controlled, crossover study in 31 healthy subjects, an absence of large mean increases (i.e., > 20 msec) was observed following 7 days of treatment with voclosporin at 0.3 mg/kg, 0.5 mg/kg and 1.5 mg/kg twice daily (approximately 6-fold coverage of the therapeutic exposure). The mechanism for the QT prolonging effect as observed in the single-dose and multiple-dose studies is unknown.

Based on data in LN patients receiving voclosporin 23.7 mg or 39.5 mg twice daily, a regression analysis of placebo corrected QTcF change from baseline showed a minimal negative slope (−0.065344 msec/ng/mL), not statistically different from a slope of 0 (p = 0.1042).

#### Clinical efficacy and safety

The safety and efficacy of voclosporin were investigated in two placebo-controlled clinical trials (AURORA 1 and AURA-LV) in patients with LN of Class III or IV (alone or in combination with Class V) or pure Class V. All patients received background therapy of MMF (2 g/day) and corticosteroids (up to a total of 1 g of intravenous (IV) methylprednisolone over days 1 and 2 followed by a starting dose of oral corticosteroids of 25 mg/day (or 20 mg/day if body weight was < 45 kg), tapered down to 2.5 mg/day by week 16.

Patients that completed the AURORA 1 study could continue in a 2-year continuation study (AURORA 2).

### Phase 3 AURORA 1

The AURORA 1 study was a phase 3, prospective, randomised, double-blind, study comparing 23.7 mg (corresponding to a 0.37 mg/kg dose) twice daily of voclosporin (n = 179) vs. placebo (n = 178) over a 52-week treatment period. The demographic characteristics of patients in the study were well balanced across the two treatment arms. The mean age was 33 years (range 18 years to 72 years) and the majority of patients were female (87.7 %), of which 81.8 % were of childbearing potential.

Most patients were White (36.1 %) or Asian (30.5 %), and approximately one third of the study population was Hispanic or Latino. The mean weight was 66.5 kg (range 36 kg to 142 kg). The median time since systemic lupus erythematosus (SLE) diagnosis was 5.0 years and the median time since LN diagnosis was 2.0 years.

Before entering the AURORA 1 study, most patients (98 %) had received treatment for LN in the past, with approximately 55 % of patients taking MMF at screening. The proportion of LN treatment naïve patients was very low (2 %).

More patients in the voclosporin arm than the placebo arm achieved the primary endpoint of renal response (table 4).

**Table 4: AURORA 1 – Summary of key efficacy endpoints**

	<b>Voclosporin (n = 179) n (%)</b>	<b>Placebo (n = 178) n (%)</b>	<b>Odds ratio vs. placebo (95 % CI)</b>	<b>p-value</b>
Renal response at week 52	73 (40.8)	40 (22.5)	2.65 (1.64, 4.27)	< 0.001
Renal response at week 24	58 (32.4)	35 (19.7)	2.23 (1.34, 3.72)	= 0.002
Partial renal response* at week 24	126 (70.4)	89 (50.0)	2.43 (1.56, 3.79)	< 0.001
Partial renal response* at week 52	125 (69.8)	92 (51.7)	2.26 (1.45, 3.51)	< 0.001

\* Partial renal response defined as a 50 % reduction in UPCR.

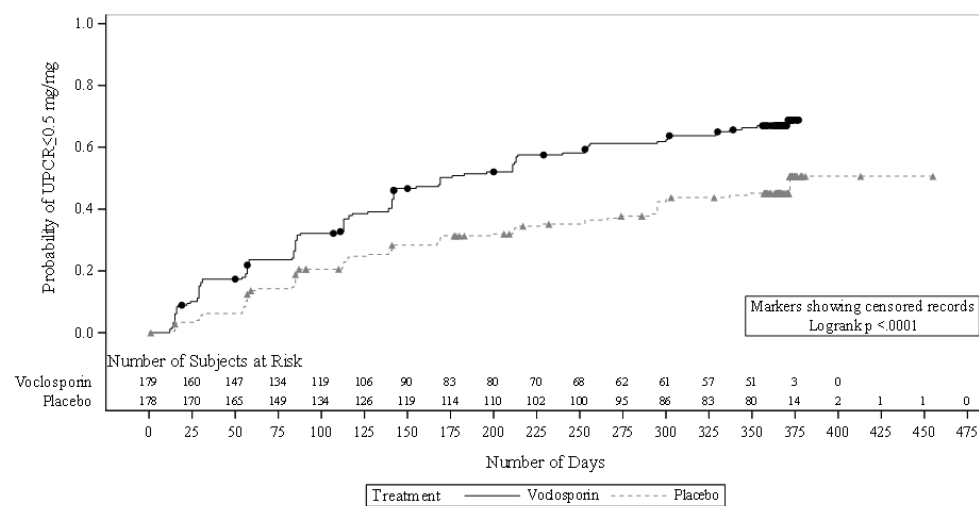
Notes: CI = Confidence interval; UPCR = Urine protein to creatinine ratio

The overall proportion of patients that achieved each of the components assessed for the primary endpoint at 52 weeks in the voclosporin vs placebo arm were:

- urine protein to creatinine ratio (UPCR)  $\leq$  0.5 mg/mg: 45.3 % vs 23.0 %
- with normal, stable renal function (defined as eGFR  $\geq$  60 mL/min/1.73 m<sup>2</sup> or no confirmed decrease from baseline in eGFR of  $>$  20 %): 82.1 % vs. 75.8 %
- in the presence of sustained, low-dose steroids (not more than 10 mg for  $\geq$  3 consecutive days or for  $\geq$  7 days in total during weeks 44 to 52): 87.2 % vs. 85.4 %
- and received no rescue medication for LN: 91.1 % vs. 86.5 %

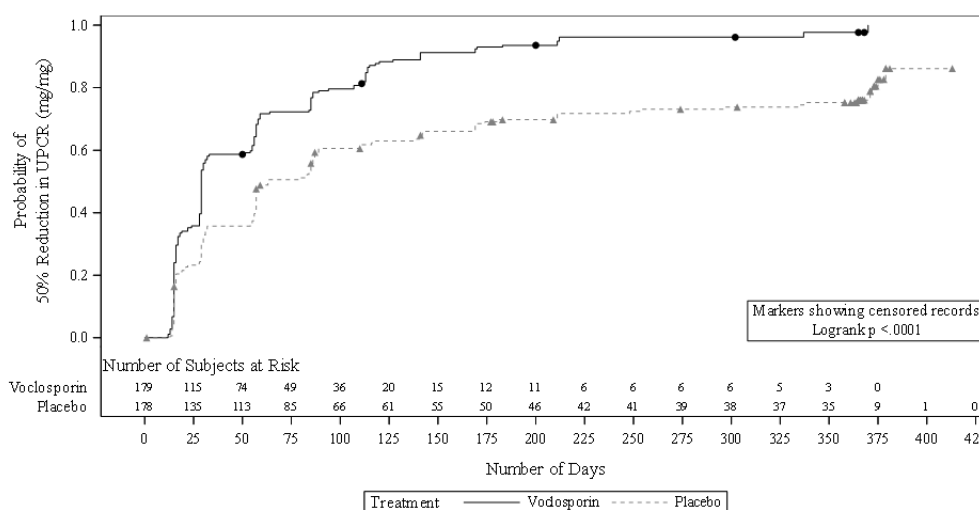
More patients in the voclosporin arm than the placebo arm achieved UPCR  $\leq$  0.5 mg/mg (64.8 % vs. 43.8 %) and the time to UPCR  $\leq$  0.5 mg/mg was significantly shorter for voclosporin treatment (median time: 169 days vs. 372 days for placebo treatment; hazard ratio (HR) 2.02; 95 % CI: 1.51, 2.70; p < 0.001).

**Figure 1: Kaplan-Meier curve of time (days) to UPCR  $\leq 0.5$  mg/mg**



The time taken to reach a 50 % reduction in UPCR was significantly shorter for the voclosporin arm than the placebo arm (HR 2.05; 95 % CI: 1.62, 2.60;  $p < 0.001$ ). Median time to 50 % reduction in UPCR was 29 days for voclosporin vs. 63 days for placebo (figure 2).

**Figure 2: Kaplan-Meier curve of time (days) to 50 % reduction in UPCR from baseline**



Over 80 % of patients in the AURORA 1 study achieved a reduction in dose of oral corticosteroid to  $\leq 2.5$  mg/day at week 24 and this dose was maintained by over 75 % of patients at week 52.

### Phase 3 AURORA 2

The AURORA 2 study was a continuation study to evaluate the long-term safety and efficacy of voclosporin in patients that completed treatment in the AURORA 1 study. Patients stayed on the same treatment and dose of voclosporin ( $n = 116$ ) or placebo ( $n = 100$ ) as at the end of AURORA 1 and continued treatment for up to a further 2 years. Over 85 % of patients completed the study (voclosporin: 87.1 %, placebo 85.0 %); 79.3 % of voclosporin patients and 73 % of placebo patients were still on study treatment at the end of study.

The proportion of patients in renal response at month 36 was 33 % (59/179) in the voclosporin group and 22 % (39/178) in the placebo group (ITT, AURORA 1) and 51 % (59/116) in the voclosporin group and 39 % (39/100) in the placebo group (ITT, AURORA 2).

## Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Lupkynis in one or more subsets of the paediatric population, in LN (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Following oral administration (voclosporin 23.7 mg twice daily) the median time to reach maximum whole blood concentrations ( $C_{max}$ ) is 1.5 hours (range: 0.75 hour to 2 hours). With a twice daily dosing regimen, voclosporin steady state is achieved after 6 days and voclosporin accumulates approximately 2-fold relative to a single dose. At steady state, the whole blood mean  $C_{max}$  and pre-dose trough values for voclosporin were 120 ng/mL (32 % CV) and 15.0 ng/mL (49 % CV), respectively. *In vitro* data investigating if voclosporin is a substrate of the efflux transporters P-gp or BCRP are inconclusive, but clinically relevant effects of P-gp/BCRP inhibitors are not expected.

Co-administration of voclosporin with food decreased both the rate and extent of absorption.  $C_{max}$  and AUC of voclosporin were reduced by 53 % and 25 % when given with high-fat food and by 29 % and 15 % when given with low-fat food. These changes were not considered to be clinically relevant. Therefore, voclosporin can be taken with or without food.

### Distribution

Voclosporin is 97 % bound to plasma proteins. Voclosporin partitions extensively into red blood cells and distribution between whole blood and plasma is concentration- and temperature-dependent. A population pharmacokinetic analysis in patients resulted in an apparent volume of distribution ( $V_{ss}/F$ ) of 2,154 L.

### Biotransformation

Voclosporin is extensively metabolised, predominantly by CYP3A4 to form oxidative metabolites. Voclosporin is the major circulating component following a single dose of [ $^{14}$ C]-voclosporin. One major metabolite was observed in human whole blood and represented 16.7 % of total exposure. The major metabolite is not expected to contribute to the pharmacological activity of voclosporin since it was reported as about 8-fold less potent in a lymphocyte proliferation assay and has lower exposure than voclosporin.

### Elimination

The mean apparent clearance at steady state ( $CL_{ss}/F$ ) after voclosporin 23.7 mg twice daily is 63.6 L/h (37.5 % CV). The mean terminal half-life ( $t_{1/2}$ ) at steady state is approximately 30 hours (range: 24.9 hours to 36.5 hours).

Following single oral administration of 70 mg [ $^{14}$ C]-voclosporin, 94.8 % of the radioactivity was recovered by 168 hours post dose: 92.7 % was recovered in faeces (including 5 % as unchanged voclosporin), and 2.1 % was recovered in urine (including 0.25 % as unchanged voclosporin).

### Linearity/non-linearity

In healthy volunteers, a non-linearity between dose and exposure was observed at the lower end of the dose range studied (0.25 mg/kg to 1.5 mg/kg twice daily), which had a relatively minor effect on the pharmacokinetics. The dose-proportionality factor was always less than 1.5. This non-linearity has not been detected over the dose range studied in LN patients.

## Pharmacokinetics in special populations

### *Renal impairment*

In clinical studies, kidney function was monitored by eGFR and doses were adjusted based on a pre-defined dose adjustment protocol. Enrolled LN patients had a baseline eGFR > 45 mL/min/1.73 m<sup>2</sup>. Dosing adjustments have to follow the recommendations outlined in table 1.

A dedicated renal impairment study revealed that after single and multiple doses of voclosporin, C<sub>max</sub> and AUC were similar in volunteers with mild (creatinine clearance (CL<sub>Cr</sub>) 60 mL/min to 89 mL/min as estimated by Cockcroft Gault) and moderate (CL<sub>Cr</sub> 30 mL/min to 59 mL/min) renal impairment compared to volunteers with normal renal function (CL<sub>Cr</sub> ≥ 90 mL/min). After a single dose of voclosporin in volunteers with severe renal impairment (CL<sub>Cr</sub> < 30 mL/min), C<sub>max</sub> and AUC increased 1.5-fold and 1.7-fold, respectively. The effect of end-stage renal disease (ESRD) with or without haemodialysis on the pharmacokinetics of voclosporin is unknown (see section 4.2).

### *Hepatic impairment*

A dedicated hepatic impairment study compared systemic exposure of voclosporin in patients with mild or moderate hepatic impairment (Child-Pugh A and B, respectively) vs. healthy controls with normal hepatic function. In patients with mild and moderate hepatic impairment, voclosporin C<sub>max</sub> and AUC<sub>0-48</sub> increased by 1.5-fold and approximately 2-fold, respectively (see section 4.2). Voclosporin has not been evaluated in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended (see section 4.4).

### *Age, sex, race and body weight*

A population pharmacokinetic analysis assessing the effects of age, sex, race and body weight did not suggest any clinically significant impact of these covariates on voclosporin exposures.

### *Lactation*

Following a single 23.7 mg dose of voclosporin in lactating volunteers (see section 4.6), an average of 0.00472 mg voclosporin was excreted in breast milk in 48h, with 80% being excreted within 12h. Data showed that the voclosporin milk to maternal blood exposure ratio was in the range of 0.42 to 0.95. For a breastmilk intake of 200 mL/kg/day, the highest relative infant dose was 1.4% of maternal weight-adjusted dose.

## **5.3 Preclinical safety data**

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Repeated-dose animal studies have shown neuro-histological findings of gliosis and perivascular infiltrates in the brain and spinal cord in rats, but not in dogs or monkeys. These findings were not observed at doses approximately 0.3-times the maximum recommended human dose (MRHD) of 23.7 mg voclosporin twice a day on medicinal product exposure (AUC) basis.

In a 39-week oral toxicology study with cynomolgus monkeys, malignant lymphomas occurred at a dose of 150 mg/kg/day (approximately 4-times and 7-times above the MRHD based on medicinal product exposure (AUC), for male and female animals, respectively). At this dose, monkeys experienced high levels of immunosuppression as indicated by maximum calcineurin inhibition levels (E<sub>max</sub>) of greater than 80 %. The no-observed-adverse-effect level (NOAEL) for this finding was 75 mg/kg/day (approximately 4-times the MRHD, on medicinal product exposure (AUC) basis, for male and female animals).

No mutagenic or genotoxic effects of voclosporin were observed in conventional genotoxicity studies.

In a 2-year mouse carcinogenicity study with oral voclosporin, an increased incidence of malignant lymphoma was observed at the highest dose tested (30 mg/kg/day; approximately 7.5-times the MRHD on a medicinal product exposure (AUC) basis). This result is considered secondary to

voclosporin-related immune suppression. The NOAEL was 10 mg/kg/day (approximately 1-times the MRHD on medicinal product exposure (AUC) basis).

In a rat fertility study with a 50:50 mixture of voclosporin and its cis-isomer, decreases in male reproductive organ weights, including the cauda epididymis, epididymis, seminal vesicles, prostate, and testes were noted at a dose of 25 mg/kg/day. The NOAEL for these findings was 10 mg/kg/day (approximately 5-times the MRHD on medicinal product exposure (AUC) basis). Mating and fertility parameters, sperm motility, count and density, number of estrous stages per 14 days, and caesarean sectioning parameters were not affected. Decreases in prostate and testes weights were also observed in the 13-week and 26-week repeat-dose toxicity studies with oral 50:50 mixture of voclosporin and its cis-isomer at doses of 25 mg/kg/day and 10 mg/kg/day, or 18-times and 7-times the MRHD, on medicinal product exposure (AUC) basis. The NOAEL for these effects in the 26-week repeat-dose study was 2.5 mg/kg/day (approximately 1-times the MRHD on medicinal product exposure (AUC) basis).

Embryo-foetal development studies were conducted with the 50:50 mixture of voclosporin and its cis-isomer in both rats and rabbits and with voclosporin in rabbits. Embryo-foetal toxicity was only observed at doses that were associated with maternal toxicity (at doses approximately 15-times and 1-times the MRHD, based upon medicinal product exposure (AUC), for rats and rabbits, respectively). The maternal effects included changes in body weight and/or swollen mammary glands while the foetal effects consisted of a slight reduction in body weight and related skeletal developmental variations. No malformative effects were noted in the studies. The NOAELs were 10 mg/kg/day in rats and 1 mg/kg/day in rabbits (approximately 7-times and 0.01-times the MRHD, based on medicinal product exposure (AUC), for rats and rabbits, respectively).

In a pre- and post-natal developmental study in rats, maternal toxicity at a dose of 25 mg/kg/day 50:50 mixture of voclosporin and its cis-isomer (approximately 17 times the MRHD on medicinal product exposure (AUC) basis) delayed parturition (dystocia) that resulted in reductions in the mean number of total pups delivered and surviving pups per litter. This dose was associated with maternal toxicity based on decreased body weight gain. No adverse effects on dams or their pups were observed at doses approximately 3-times the MRHD and lower (based on medicinal product exposure (AUC) with a maternal oral NOAEL dose of 10 mg/kg/day). There were no effects on behavioural and physical development, or the reproductive performance of male or female pups. The no effect dose for delivery and pup survival was 10 mg/kg/day.

Medicinal product-derived radioactivity was rapidly distributed to milk following the oral administration of [ $^{14}\text{C}$ ]-voclosporin to lactating rats. When a medicinal product is present in animal milk, it is likely that it will also be present in human milk.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content

Ethanol  
Vitamin E (E307) polyethylene glycol succinate (tocofersolan)  
Polysorbate 40  
Medium-chain triglycerides

#### Capsule shell

Gelatin  
Sorbitol

Glycerin  
Purified water  
Titanium dioxide (E171)  
Iron oxide, red (E172)  
Iron oxide, yellow (E172)

#### Processing aids

Soya lecithin

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

4 years

### **6.4 Special precautions for storage**

Store in the original blister in order to protect from moisture.

### **6.5 Nature and contents of container**

Soft capsules are available in cold-formed aluminium blisters, laminated backing and lidding materials that are thermo-sealed together. Each blister contains 18 soft capsules. One carton contains 180 or 576 soft capsules.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Otsuka Pharmaceutical Netherlands B.V.  
Herikerbergweg 292  
1101 CT Amsterdam  
Netherlands

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1678/001 (180 soft capsules)  
EU/1/22/1678/002 (576 soft capsules)

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 15 September 2022



## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu/>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Limited  
Block-7, City North Business Campus, Stamullen, Co. Meath, K32 YD60,  
Ireland

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Lupkynis 7.9 mg soft capsules  
voclosporin

**2. STATEMENT OF ACTIVE SUBSTANCE**

Each soft capsule contains 7.9 mg of voclosporin.

**3. LIST OF EXCIPIENTS**

Contains alcohol (ethanol), sorbitol and may contain trace amounts of soya lecithin.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Soft capsule  
180 soft capsules  
576 soft capsules

**5. METHOD AND ROUTE OF ADMINISTRATION**

Oral use.  
Swallow soft capsules whole.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original blister in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Otsuka Pharmaceutical Netherlands B.V.  
Herikerbergweg 292  
1101 CT Amsterdam  
Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1678/001 (180 soft capsules)  
EU/1/22/1678/002 (576 soft capsules)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

lupkynis 7.9 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER</b>
----------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Lupkynis 7.9 mg capsule  
voclosporin

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Otsuka

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------



## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the patient**

### **Lupkynis 7.9 mg soft capsules**

voclosporin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Lupkynis is and what it is used for
2. What you need to know before you take Lupkynis
3. How to take Lupkynis
4. Possible side effects
5. How to store Lupkynis
6. Contents of the pack and other information

#### **1. What Lupkynis is and what it is used for**

Lupkynis contains the active substance voclosporin. It is used for the treatment of adults from 18 years of age with lupus nephritis (inflammation of the kidney caused by lupus).

The active ingredient in Lupkynis is one of a group of medicines known as calcineurin inhibitors that can be used to control your body's immune response (immunosuppressants). In lupus, the immune system (the body's natural defences) mistakenly attacks parts of your own body, including the kidneys (lupus nephritis). By reducing the response of the immune system, the medicine reduces inflammation of your kidneys and lessens symptoms such as swelling of the legs, ankles or feet, high blood pressure, tiredness, as well as improving your kidney function.

#### **2. What you need to know before you take Lupkynis**

##### **Do not take Lupkynis**

- If you are allergic to voclosporin or any of the other ingredients of this medicine (listed in section 6).
- If you are taking other medicines such as ketoconazole tablets (used to treat Cushing's syndrome when the body produces an excess of cortisol), itraconazole or clarithromycin (used to treat certain fungal and bacterial infections).

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Lupkynis if any of the following applies to you:

- if your kidney disease gets worse, your dose of this medicine may need to be changed. Your doctor will regularly check how well your kidneys are working.
- if you have risk factors for pure red cell aplasia (PRCA) – a rare disorder in which the bone marrow does not make enough red blood cells. Such risk factors are a former infection with parvovirus B19 or other treatments in the past that may cause PRCA.

- if you suffer from or develop high blood pressure. Your doctor will check your blood pressure every two weeks for the first month and then regularly. He/she may give you a medicine to lower your blood pressure or tell you to stop taking this medicine.
- This medicine can increase the risk of conditions of the nervous system, such as headache, shaking, changes in vision, seizures, confusion or weakness in one or more limbs. If you experience any of these new symptoms or worsening of existing symptoms, your doctor may consider stopping or lowering the dose of this medicine (see section 4).
- if you are planning to have a vaccination or have had a vaccination within the last 30 days. This medicine may affect the response to vaccination, and vaccination during treatment with this medicine may be less effective.
- if you have previously experienced sudden life-threatening allergic reactions (anaphylactic reactions) to soya or peanut, do not take this medicine.

This medicine can increase the potassium levels in your blood, which may be serious and require treatment. Your doctor will check your potassium levels periodically during treatment.

This medicine has not been studied in patients with severe liver problems and is therefore not recommended in these patients.

This medicine may influence the electrical activity of your heart (QT prolongation). This can result in serious heart rhythm disorder. Early symptoms are dizziness and fainting.

### **Sunlight and UV light**

This medicine can increase the risk of developing certain types of cancer, particularly of the skin. You should avoid or limit your exposure to sunlight and UV light by wearing appropriate protective clothing and frequently applying sunscreen with a high protection factor.

### **Infections**

This medicine can increase your risk of developing infections, some of which may be serious or even fatal. Contact your doctor if you have any signs of infection, such as fever, chills or sore throat. Your doctor will decide whether you need to stop taking this medicine (see section 4).

### **Children and adolescents**

Do not take this medicine if you are under the age of 18 years because it has not been studied in this age group.

### **Elderly**

This medicine is not recommended if you are over the age of 75 years because it has not been studied in this age group.

### **Other medicines and Lupkynis**

Tell your doctor or pharmacist if you are taking or have recently taken or are planning to take any other medicines.

In particular, tell your doctor if you take:

- Medicines used to treat fungal infection such as itraconazole and fluconazole.
- Medicines used to treat Cushing's syndrome (when the body produces an excess of cortisol), such as ketoconazole tablets.
- Medicines used to treat high blood pressure or heart problems such as digoxin, diltiazem and verapamil.
- Medicines to prevent the formation of blood clots such as dabigatran etexilate.
- Medicines used to treat epilepsy such as carbamazepine and phenobarbital.
- Herbal preparations containing St. John's Wort, used to treat mild depression.
- Medicines for the relief of symptoms associated with seasonal allergic rhinitis such as fexofenadine.
- Antibiotic medicines used to treat bacterial infections such as rifampicin, clarithromycin and erythromycin.

- Medicines that lower cholesterol such as simvastatin, atorvastatin, rosuvastatin and pravastatin.
- Medicines used to treat HIV infections, such as the antiretroviral efavirenz.

### **Lupkynis with food and drink**

This medicine can be taken with or without food. Avoid eating grapefruit and drinking grapefruit juice during treatment with this medicine, since these can affect how the medicine works.

### **Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

This medicine is not recommended during pregnancy and in women of childbearing potential not using contraception.

Tell your doctor if you are breast-feeding. This medicine can pass into breast milk and it is not known if this medicine can affect your baby. Your doctor will discuss with you whether to stop treatment with this medicine while you are breast-feeding, or to stop breast-feeding.

There are no data on the effect of this medicine on human fertility.

### **Driving and using machines**

Lupkynis is not expected to have any effect on your ability to drive and use machines.

### **Lupkynis contains alcohol**

This medicine contains 21.6 mg of alcohol (ethanol) in each capsule. Therefore, a dose of 3 capsules of Lupkynis contains 64.8 mg ethanol, which is equivalent to less than 2 mL beer or 1 mL wine. This small amount of alcohol in this medicine will not have any noticeable effects.

### **Lupkynis contains sorbitol**

This medicine contains 28.7 mg of sorbitol in each capsule.

### **Lupkynis may contain soya lecithin**

This medicine may contain trace amounts of soya lecithin. If you experience anaphylactic reactions to soya or peanut, you must not use this medicine.

## **3. How to take Lupkynis**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Lupkynis is three capsules twice daily, taken by mouth.

The capsules must be swallowed whole and can be taken with or without food.

Take the daily doses at around the same time each day, at least 8 hours apart and ideally as close to 12 hours apart as possible (for example, at 8:00 am in the morning and 8:00 pm in the evening).

This medicine should be used in combination with another immunosuppressant medicine, mycophenolate mofetil.

### **If you take more Lupkynis than you should**

If you have accidentally taken too many capsules, contact your doctor or nearest hospital emergency department immediately. Symptoms of overdose may include a fast heartbeat and tremors (uncontrolled shaking or trembling in one or more parts of the body).

**If you forget to take Lupkynis**

If a dose is missed, take it as soon as possible and within 4 hours of missing the dose. If more than 4 hours have passed since the time you normally take the medicine, just skip that dose and take the next regular dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Lupkynis**

Do not stop your treatment unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Serious side effects**

If any of these occur, seek immediate medical advice as your doctor may advise you to stop taking this medicine or reduce the dose.

**Very common** (may affect more than 1 in 10 people)

- Symptoms of infection (such as fever, body aches, feeling tired, coughing or sneezing, nausea, vomiting or diarrhoea)

**Common** (may affect up to 1 in 10 people)

- Newly developing symptoms of nerve or brain problems, such as seizures

**Other side effects****Very common** (may affect more than 1 in 10 people)

- Upper chest infection
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Headache
- Increased blood pressure
- Cough
- Diarrhoea
- Pain in the abdomen (belly)
- Changes in your kidney function which could reduce the amount of urine you produce and may cause new or worsening swelling in your legs or feet

**Common** (may affect up to 1 in 10 people)

- Fever, cough, difficult or painful breathing, wheezing, pain in chest when breathing (possible symptoms of pneumonia)
- Infections, that can either be bacterial such as urinary tract infections or viral such as shingles
- Inflammation of the stomach and intestines
- Flu
- Increased levels of potassium seen in blood test
- Decreased appetite
- Tremors
- Feeling sick
- Abnormal swelling, bleeding and/or inflammation of the gums
- Ulcers of mouth
- Indigestion
- Hair loss
- Excessive and/or abnormal hair growth on any part of the body

- Tiredness

**Not known** (frequency cannot be estimated from the available data)

- Hypersensitivity

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Lupkynis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after “EXP”.

The expiry date refers to the last day of that month.

Store in the original blister in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Lupkynis contains

- The active substance is voclosporin. Each soft capsule of Lupkynis contains 7.9 mg of voclosporin.
- The other ingredients are:  
*Capsule content:* ethanol, vitamin E (E307) polyethylene glycol succinate (tocofersolan), polysorbate 40 and medium-chain triglycerides  
*Capsule shell:* gelatin, sorbitol, glycerin, purified water, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)  
*Processing aid:* soya lecithin

### What Lupkynis looks like and contents of the pack

Lupkynis 7.9 mg pink/orange, soft capsules measuring approximately 13 mm × 6 mm packed in blisters. Each blister contains 18 soft capsules. One carton contains 180 or 576 soft capsules.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder

Otsuka Pharmaceutical Netherlands B.V.  
 Herikerbergweg 292  
 1101 CT Amsterdam  
 Netherlands

### Manufacturer

Millmount Healthcare Limited  
 Block-7, City North Business Campus, Stamullen, Co. Meath, K32 YD60,  
 Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### België/Belgique/Belgien

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 Tél/Tel: +46 (0) 8 545 286 60

#### Lietuva

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**България**

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**Česká republika**

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:

<https://www.ema.europa.eu/>. There are also links to other websites about rare diseases and treatments.



#### **ANNEX IV**

#### **SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)**

## **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for voclosporin, the scientific conclusions of PRAC are as follows:

In view of available data on fatigue from clinical trials, spontaneous reports including in 237 cases with a close temporal relationship, 10 cases with positive de-challenge, the PRAC considers a causal relationship between voclosporin and fatigue is at least a reasonable possibility. The PRAC concluded that the product information of products containing voclosporin should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

## **Grounds for the variation to the terms of the Marketing Authorisation(s)**

On the basis of the scientific conclusions for voclosporin the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing voclosporin is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.