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^2. If eGFR remains ≥ 60 mL/min/1.73 m^2 no dose modification is required (see table 1).

Table 1: Recommended dose adjustments based on eGFR

Confirmed eGFR decrease from baseline[1]	**Recommendation**
≥ 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.
≤ 20 % reduction	Maintain current dose and monitor.

[1] If eGFR remains ≥ 60 mL/min/1.73 m^2 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 ≥ 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^2. 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^2) 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

Blood pressure	**Recommendation**
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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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
Infections and infestations	Upper respiratory tract infection[1]	Pneumonia Influenza Herpes zoster Gastroenteritis Urinary tract infection	
Blood and lymphatic system disorders	Anaemia		
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Hyperkalaemia Decreased appetite	
Nervous system disorders	Headache	Seizure Tremor	
Vascular disorders	Hypertension[2]		
Respiratory, thoracic and mediastinal disorders	Cough		
Gastrointestinal disorders	Diarrhoea Abdominal pain[3]	Nausea Gingival hyperplasia[4] Dyspepsia Mouth ulceration	
Skin and subcutaneous tissue disorders		Alopecia Hypertrichosis[5]	
Renal and urinary disorders	Glomerular filtration rate decreased[6,7]	Acute kidney disease[6] Acute kidney injury[6]	
General disorders and administration site conditions		Fatigue	

[1] Includes the following Preferred Terms (PTs): viral upper respiratory tract infection and upper respiratory tract infection bacterial
[2] Includes the following PTs: blood pressure increased, blood pressure diastolic increased, diastolic hypertension
[3] Includes the following PTs: abdominal pain upper, abdominal discomfort
[4] Includes the following PTs: gingivitis, gingival bleeding, gingival hypertrophy, gingival swelling
[5] Includes the following PTs: hypertrichosis, hirsutism
[6] Includes the PT renal impairment
[7] 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 ≥ 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 ≥ 20 %. Similarly for patients with an eGFR decrease of ≥ 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

	Voclosporin (n = 179) n (%)	Placebo (n = 178) n (%)	Odds ratio *vs.* placebo (95 % CI)	p-value
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.

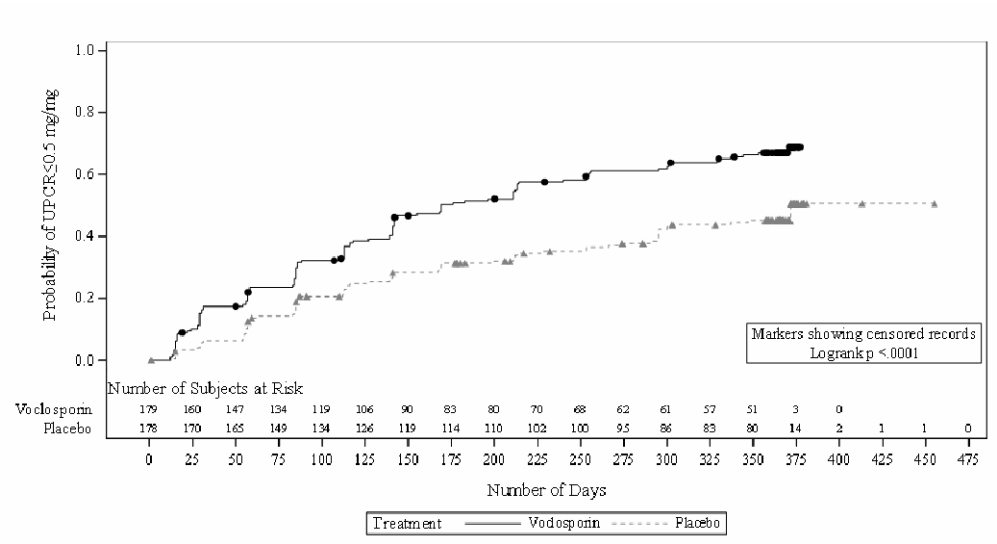
Notes: CI = Confidence interval; UPCR = Urine protein to creatinine ratio

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) ≤ 0.5 mg/mg: 45.3 % vs 23.0 %
- with normal, stable renal function (defined as eGFR ≥ 60 mL/min/1.73 m^2 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 ≥ 3 consecutive days or for ≥ 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 %

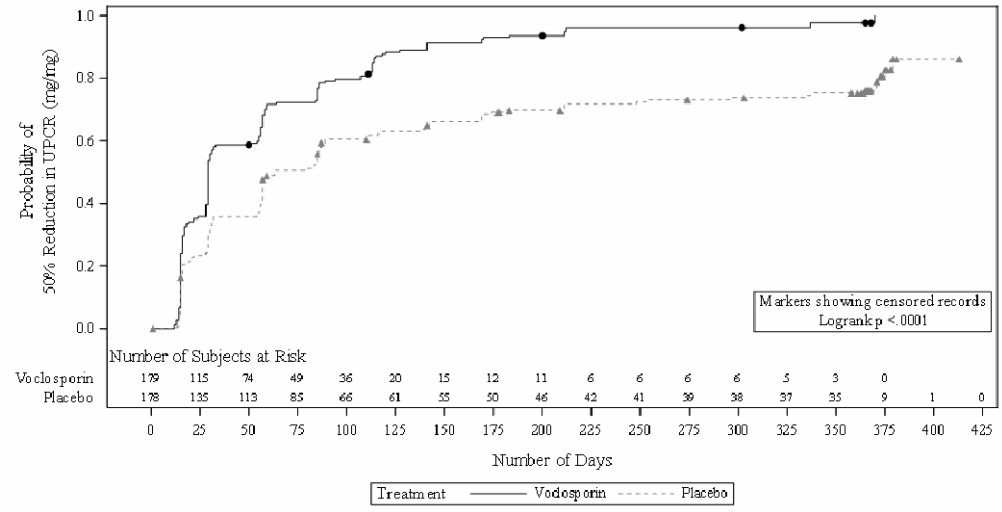
More patients in the voclosporin arm than the placebo arm achieved UPCR ≤ 0.5 mg/mg (64.8 % *vs.* 43.8 %) and the time to UPCR ≤ 0.5 mg/mg was significantly shorter for voclosporin treatment (median time: 169 days *vs.* 372 days for placebo treatment; hazard ratio (HR) 2.02; 95 % CI: 1.51, 2.70; p <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

Figure 1: Kaplan-Meier curve of time (days) to UPCR ≤ 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 ≤ 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 ($t_{½}$) 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^2. 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_{max} and AUC were similar in volunteers with mild (creatinine clearance (CL_{Cr}) 60 mL/min to 89 mL/min as estimated by Cockcroft Gault) and moderate (CL_{Cr} 30 mL/min to 59 mL/min) renal impairment compared to volunteers with normal renal function ($CL_{Cr} \geq 90$ mL/min). After a single dose of voclosporin in volunteers with severe renal impairment ($CL_{Cr} < 30$ mL/min), C_{max} 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_{max} and AUC_{0-48} 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_{max}) 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}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

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10 DATE OF REVISION OF THE TEXT

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