swissmedic

Date: 7 August 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lupkynis

International non-proprietary name: voclosporin
Pharmaceutical form: soft capsule
Dosage strength(s): 7.9 mg
Route(s) of administration: oral
Marketing authorisation holder: Otsuka Pharmaceutical
Marketing authorisation no.: 68697
Decision and decision date: approved on 24 April 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	*bis in die*, twice daily
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNI	Calcineurin inhibitor
CYP	Cytochrome P450
DDI	Drug-drug interaction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESRD	End-stage renal disease
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LN	Lupus nephritis
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MMF	Mycophenolate mofetile
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SLE	Systemic lupus erythematosus
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UPCR	Urine protein/creatinine ratio

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for voclosporin in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 24 February 2022.

2.2 Indication and dosage

2.2.1 Requested indication

Lupkynis is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with lupus nephritis.

2.2.2 Approved indication

Lupkynis is indicated in combination with a background immunosuppressive therapy for the treatment of adult patients with active class III, IV, or V (including mixed classes III/V and IV/V) lupus nephritis (see "Dosage/Administration" and "Clinical Efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Lupkynis is 23.7 mg (3 x 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 doses on an empty stomach. 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 Lupkynis therapy. Dose adjustments are required for those patients whose estimated glomerular filtration rate (eGFR) is confirmed to be reduced.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	4 October 2021
Formal control completed	26 October 2021
List of Questions (LoQ)	15 February 2022
Response to LoQ	13 June 2022
Preliminary decision	25 August 2022
Response to preliminary decision	20 October 2022
Labelling corrections	29 December 2022
Response to labelling corrections	24 January 2023
Final decision	24 April 2023
Decision	approval

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3 Medical context

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease, typically affecting female patients of 20 to 40 years of age. Its most common serious manifestation, lupus nephritis (LN), affects about 50-60% of patients with SLE, of whom nearly one-third ultimately progress to end-stage renal disease (ESRD) with the chronic need for dialysis. The International Society of Nephrology and the Renal Pathology Society discriminate six LN classes (I to VI) which are relevant for the prognosis of the disease.

Current treatment options for LN are still unsatisfactory, with high-dose corticosteroids plus off-label use of an immunosuppressant. In August 2021, belimumab – initially approved for the treatment of SLE in Switzerland in 2012 – received approval for the treatment of LN.

Voclosporin is a novel calcineurin inhibitor (CNI), which is structurally similar to cyclosporin A except for the modification of a functional group on amino acid-1 of the molecule. This alteration seems to enhance the binding of voclosporin to calcineurin and has been shown in both in vitro and in vivo animal studies to increase the potency by two- to five-fold compared to cyclosporin A. This modification has several advantages over cyclosporin A, including faster elimination, a predictable PK/PD relationship, and fewer CNI-associated side effects.

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4 Quality aspects

4.1 Drug substance

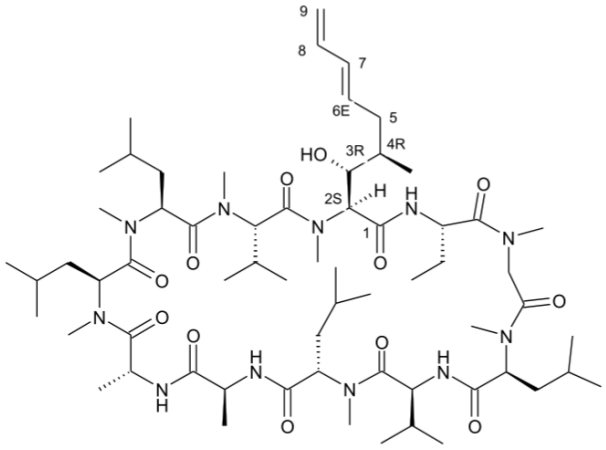
INN: Voclosporin

Chemical name: Cyclo{[(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-((methylamino)-6,8-nonadienoyl]-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}.

Molecular formula: $C_{63}H_{111}N_{11}O_{12}$

Molecular mass: 1214.6 g/mol

Molecular structure:



Physico-chemical properties:

White to off-white solid matter; practically insoluble in water; freely soluble in acetone, acetonitrile, ethanol, and methanol; practically insoluble in heptane. Slightly hygroscopic. Chiral cyclosporin derivative containing 12 asymmetric centres and a C=C double bond (C6 to C7 as depicted above) which predominantly exists as the E (trans) configuration.

Synthesis:

Semi-synthetic product, synthesised by chemical modification of a substance originally manufactured by fermentation. The chemical synthesis consists of several steps and a final purification step.

Specification:

In order to ensure consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:

Appropriate stability data have been presented. Based on the results, satisfactory re-test periods have been established when stored in tight packaging proposed in the application.

4.2 Drug product

Description and composition:

The drug product consists of a non-aqueous solution of voclosporin drug substance, containing 7.9 mg of voclosporin drug substance per unit, filled into a size 5 opaque pink-orange to orange soft gelatin capsule. Softgel capsules are packaged in blister strips composed of cold-formed aluminium foil/aluminium foil push lidding. Blister strips are packaged in a carton.

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Pharmaceutical development:

Softgel capsule was chosen as the dosage form in order to adequately protect and administer the active ingredient. Voclosporin is administered as a non-aqueous solution, along with suitable excipients in the capsule fill, promoting its solubilisation and finally its bioavailability.

Manufacture:

Lupkynis capsules are manufactured in several process steps. The gelatin mass is prepared separately and then introduced into the encapsulation process, along with the capsule fill, followed by drying, washing, sorting, and metal checking.

Specification:

For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include relevant physicochemical characteristics, identification of the drug substance, as well as assay and purity tests.

Container closure system:

The capsules are packed in aluminium foil blisters.

Stability:

Appropriate stability data have been generated for the product packed in aluminium blisters, according to the relevant international guidelines. The storage recommendations are “Do not store above 25°C”, and to keep the product in its original container in order to protect it from moisture.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

Regarding the marketing authorisation application for Lupkynis, the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the FDA assessment report provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Lupkynis in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The safety issues identified in the nonclinical studies that would be of concern for human use are described in the RMP. The safety margins are low. However, this can be accepted considering the similarity of toxicological findings between voclosporin and cyclosporin.

The nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

Voclosporin does not represent a risk for the environment at the prescribed dose.

There are no concerns with impurities or excipients.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on a previous regulatory decision by the FDA. The available assessment report and corresponding product information from the FDA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose finding and dose recommendation

To find the optimal dose of voclosporin, multiple phase 1 and phase 2 studies have been conducted in various indications, including renal transplants but not LN, establishing 23.7 mg BID to be the most favourable dose. Doses lower than 23.7 mg BID did not demonstrate sufficient efficacy.
The multi-centre, randomised, double-blind phase 2 study AURA-LV compared the treatment effect (clinical remission defined as decrease in proteinuria [UPCR ≤ 0.5 mg/mg] AND lack of decline in eGFR below 60 ml/min/1.73m^2 or by ≥ 20% from baseline) of two dosages of voclosporin (23.7 mg BID and 39.5 mg BID) in 265 patients with LN (and without the use of rescue medications) at Week 24 (primary endpoint) and Week 48 (key secondary endpoint). The study demonstrated a statistically significant benefit for the lower dose after 6 and 12 months compared to background immunosuppressive treatment only, but for the higher dose only after 12 months. Based on these data, the selection of the 23.7 mg BID dose for further investigation in the phase 3 studies can be endorsed.
Voclosporin shows a certain dose-dependency in regard to the occurrence of adverse events, therefore, a lower than 23.7 mg BID dose, e.g. 15.8 mg BID as proposed in the information for healthcare professionals for patients with hepatic impairment or in case of a relevant decrease in eGFR on treatment, could be more favourable. Further, almost half of the pivotal studies' patients required a temporary dose reduction due to adverse events (mostly temporary decrease in eGFR), but lowering the dose results in a substantially lower efficacy. Although overall the data leave some uncertainty on whether a lower dose may not have been better, the efficacy and safety of a 23.7mg dose were confirmed in the pivotal studies.

6.3 Efficacy

Efficacy was investigated in two pivotal studies: AURORA 1 (first 52 weeks of treatment), and AURORA 2 (long-term extension for another 2 years).
In AURORA 1, a multi-centre, randomised, double-blind placebo-controlled study, voclosporin 23.7 mg BID was studied compared to placebo in 357 patients with LN of the classes III, IV, V or the mixed classes III/V and IV/V all being treated with background MMF and corticosteroids. The primary endpoint was complete renal response at Week 52 (identical to "clinical remission" in study AURA-LV, see above). The proportion of patients achieving a complete renal response at Week 52 was significantly larger in the voclosporin 23.7 mg BID arm than in the placebo control (40.8 % vs 22.5 %), with an odds ratio of 2.6 (95 % CI: 1.6, 4.3). The results from the analyses of the subcomponents of both the complete renal response endpoints, and from analyses of secondary endpoints, supported those of the primary analysis. The wording of the indication was adjusted to reflect that only patients with LN classes III, IV, V (and mixed classes III/V or IV/V) were included in the pivotal studies and hence efficacy was only demonstrated in those patients.
AURORA 2 was an extension study that enrolled 216 patients who had completed AURORA 1 for continuation of their randomised treatment for up to 24 additional months. This study demonstrated a sustained – and compared to placebo statistically significantly greater – clinical response in LN patients treated with voclosporin for up to 36 months in total (complete renal response after 18, 24, 30, and 36 months was [voclosporin vs. placebo] 63.8% vs 46.0%, 56.0% vs. 43.0%, 59.5% vs. 42.0%, 59.5% vs. 42.0%, and 50.9% vs 39.0%, respectively).
The only approved competitor is belilumab, for which no comparative data is available. In comparison to belimumab, voclosporin offers a slightly more unfavourable safety profile, although cross-study

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comparisons should be made with caution due to different populations, and endpoints in the pivotal studies.

For further details, please refer to the information for healthcare professionals.

6.4 Safety

In the study programme, 365 LN patients were exposed to voclosporin, and in total (all indications included), 2,666 patients were exposed to voclosporin. Safety data for the first year of treatment originate from studies AURA-LV and AURORA 1, safety data for the first 3 years of treatment from study AURORA 2.

The majority of patients treated with voclosporin completed the studies. Fewer patients treated with voclosporin discontinued treatment prematurely compared to patients treated with placebo (26.9% vs. 32.0% within the first year), adverse events being the most common reason for discontinuation on both treatments. The fraction of patients discontinuing treatment with voclosporin because of adverse events declined over time (within the first year of treatment: 13.5%, within years 2 and 3 of treatment: 9.5%).

The most common adverse events were nephrotoxicity, hypertension, and decreased eGFR. In roughly one in two patients treated with voclosporin, nephrological adverse events led to a – mostly temporary – decrease in dosage. Corresponding warnings are therefore included in the “warnings and precautions” section of the information for healthcare professionals. Other common adverse events were infections and infestations, and gastrointestinal disorders. Long-term treatment with voclosporin for up to 3 years demonstrated a similar safety profile compared to the first year of treatment, and especially seems not to increase the risk of serious infections.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Voclosporin is a novel calcineurin inhibitor for treatment of LN, which is a very common and potentially life-threatening complication of SLE. Outcomes with the current standard of care – background therapy with corticosteroids combined with off-label immunosuppressive therapy – remain unsatisfactory.

Analysis of the efficacy data demonstrated superiority of voclosporin treatment versus placebo in subjects with lupus nephritis receiving background treatment with MMF and corticosteroids. The pivotal phase 3 study AURORA 1 robustly demonstrated an increased proportion of patients achieving a complete renal response at Week 52. The AURORA 2 study proved the sustained nature of this treatment benefit for a follow-up period of 2 years. Given that no comparative data from the pivotal studies are available, it is unclear how efficacy and safety of voclosporin compare to belimumab.

Two CNI-related adverse events (nephrotoxicity and hypertension) accounted for the majority of the adverse events, and decrease in eGFR was common. Approximately 46% of voclosporin-treated subjects experienced a nephrological adverse event that necessitated a protocol-specified dosage modification compared to 25% of placebo-treated subjects. These adverse events are therefore reflected in the “warnings and precautions” section of the information for healthcare professionals. Infections and infestations were common, but the risk for serious infections did not increase significantly in the long-term. Long-term data from AURORA 2 indicate that discontinuation rates do not increase drastically over time (9.5% after 3 years vs. 7.5% after 1 year), and the overall safety profile is similar in the long-term compared to the first year of treatment.

The clinical data compellingly prove voclosporin’s treatment benefit (clinical remission / complete renal response) in patients with LN of the studied classes III, IV, V (including mixed classes III/V and IV/V) for at least 36 months. The safety profile of voclosporin is governed by nephrotoxicity, hypertension, and decrease in eGFR, partially forcing dose reductions, and infections. Overall, the

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demonstrated benefit of voclosporin in combination with corresponding statements of the potential risks in the information for healthcare professionals outweigh the aforementioned safety issues.

The benefit-risk-assessment for voclosporin in the indication of active lupus nephritis classes III, IV or V (including mixed class III/V and IV/V) in adult patients in combination with MMF and corticosteroids is positive.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Lupkynis was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Lupkynis

Composition

Active substances

Voclosporin

Excipients

Capsule contents: Ethanol, Tocofersolan; Polysorbate 40; Medium-chain triglycerides

Capsule shell: Gelatin; Sorbitol [E420] from a glycerin blend; Titanium dioxide [E171]; E172 (Iron oxide red, yellow); Purified water q.s.

Each soft capsule contains 21.6 mg ethanol and 28.7 mg sorbitol.

Pharmaceutical form and active substance quantity per unit

Soft capsule: Pink/orange, oval soft capsule (approximately 13 mm x 6 mm)
Each soft capsule contains 7.9 mg voclosporin.

Indications/Uses

Lupkynis is indicated in combination with a background immunosuppressive therapy for the treatment of adult patients with active class III, IV, or V (including mixed classes III/V and IV/V) lupus nephritis (see “Dosage/Administration” and Clinical Efficacy”).

Dosage/Administration

General information

Treatment with Lupkynis should be initiated and monitored by a physician experienced with immunosuppressive therapy for the treatment of SLE/lupus nephritis, and can provide adequate follow-up, including regular full physical examination, monitoring of blood pressure and control of laboratory safety parameters.
The background therapies used in the clinical studies were mycophenolate mofetil (MMF) and corticosteroids (see “Properties/Effects”/”Clinical efficacy”). The safety and efficacy of Lupkynis in combination with other immunosuppressives (including cyclophosphamide) has not been studied.

Usual dosage

The recommended dose of Lupkynis 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 doses. 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, it shall be waited until the usual scheduled time to take the next regular dose. Do not double the next dose.

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 Lupkynis therapy.

Dose adjustment/titration

It is recommended to establish a baseline estimated glomerular filtration rate (eGFR) before starting treatment with Lupkynis, 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 Lupkynis. Restart Lupkynis upon eGFR recovery at a lower dose and increase as tolerated based on renal function.
> 20% and < 30% reduction	Reduce dose of Lupkynis by 7.9 mg twice daily. Retest within two weeks, if eGFR decrease has not recovered, reduce dose by further 7.9 mg twice daily.
≤ 20% reduction	Maintain current dose of Lupkynis 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, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥ 80% of baseline; do not exceed the starting dose.

When co-administering Lupkynis with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem), reduce Lupkynis daily dosage to 15.8 mg in the morning and 7.9 mg in the evening (see “Interactions”).

Special dosage instructions

Patients with hepatic disorders

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 is not recommended in this patient population (see “Warnings and precautions” and “Pharmacokinetics”).

Patients with renal disorders

Voclosporin undergoes minimal renal elimination and its pharmacokinetics are not extensively affected by renal impairment. However, careful monitoring of renal function is recommended (see Table 1 and “Warnings and precautions”). It is recommended to only use Lupkynis in patients with baseline eGFR 30 to < 45 mL/min/1.73 m^2, 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 “Pharmacokinetics”).

Elderly patients

Limited information is available on elderly patients with LN. Population pharmacokinetic analyses showed that age (range 18 to 66 years) does not have a meaningful influence on the exposure of voclosporin.

Children and adolescents

The safety and efficacy of Lupkynis in children below the age of 18 years have not yet been established. No data are available.

Mode 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 “Interactions”).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Co-administration of voclosporin with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) (see “Interactions”).

Warnings and precautions

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 (e.g., tuberculosis, cytomegalovirus infection and herpes zoster infection) which may be serious or fatal. 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

The risk of acute and/or chronic nephrotoxicity is increased when Lupkynis is co-administered with medicinal products associated with nephrotoxicity.
Like 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. This can be managed by dose adjustments. Regular monitoring of eGFR levels is recommended (see "Dosage/Administration").

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. 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. 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

QTc interval prolongation

Lupkynis results in dose-dependent prolongation of the QTc interval (on average up to 34.6ms) after a single dose higher than the recommended therapeutic dose (see "Properties and Effects", Pharmacodynamics). Use of Lupkynis in combination with other medicinal products known to prolong the QTc interval may result in a clinically significant QTc prolongation. Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with use of medicinal products that prolong the QTc interval, including bradycardia, hypokalaemia or hypomagnesaemia, concurrent use of other medicinal products that prolong the QTc interval and the presence of a congenital prolongation of the QT interval. For patients with increased risk of QT prolongation, consider obtaining ECG and monitoring electrolytes.

Neurotoxicity

Patients receiving immunosuppressive therapies, including voclosporin, are at increased risk of neurotoxicity (see "Undesirable effects"). Monitor patients for neurotoxicity and consider reduction or

discontinuation of voclosporin if new-onset neurological symptoms occur including posterior reversible encephalopathy syndrome (PRES), seizure or tremors.

Hepatic Impairment

Voclosporin has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it should not be used in this patient population.

Vaccination

No data are available on the response to live vaccinations in patients treated with voclosporin. Immunosuppressants may affect the response to vaccination, and vaccination during treatment with voclosporin may be less effective. Currently available data do not allow an assessment of whether voclosporin inhibits the immune response to neo-antigens and/or booster antigens. Vaccinations should be up to date and any required vaccinations should be given prior to start of treatment, if possible. The use of live attenuated vaccines should be avoided during use of voclosporin. The benefit-risk balance should be considered prior to administering vaccines during voclosporin treatment.

Foods and medicinal products that affect CYP3A4

Voclosporin is metabolised in the liver, mainly via CYP3A4. Intake of voclosporin concurrently with moderate to potent inducers (e.g. St. John's wort) or with grapefruit and grapefruit juice is not recommended (see "Interactions").

Soya Lecithin (potential residue of manufacturing)
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.

Excipients with particular interest

Each Lupkynis soft capsule contains 21.6 mg of ethanol. A daily dose of 47.4 mg of Lupkynis (six soft capsules containing 7.9 mg) contains 129.6 mg ethanol. The small amount of alcohol in this medicine will not have any noticeable effects.

Each Lupkynis soft capsule contains 28.7 mg of sorbitol. A daily dose of 47.4 mg of Lupkynis (six soft capsules containing 7.9 mg) contains 172.2 mg sorbitol. The additive effect of concomitantly administered medicinal 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.

Interactions

Effect of other agents on the pharmacokinetics of voclosporin

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.

Concomitant use contraindicated

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 "Contraindication").

Concomitant use not recommended

CYP3A4 inducers
Voclosporin exposure was 87% lower in the presence of the strong CYP3A4 inducer rifampicin compared to voclosporin administration alone. Co-administration of multiple doses of the moderate CYP3A4 inducer efavirenz was predicted to decrease voclosporin exposure by 70%.
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 "Warnings and precautions").

Other interactions

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

Although weak CYP3A4 inhibitors may increase voclosporin exposure, the effect is not considered to be clinically relevant (less than 1.25-fold). No dose adjustment is required when voclosporin is co-administered with weak CYP3A4 inhibitors.

Effect of voclosporin on the pharmacokinetics of other agents

P-gp substrates
Voclosporin is a weak inhibitor of P-glycoprotein (P-gp) and caution is advised for co-administration of voclosporin with sensitive P-gp substrates. Concomitant administration of voclosporin with multiple doses of digoxin increased digoxin C_{max} and AUC by 1.51-fold and 1.25-fold, respectively. Since digoxin is considered to have a narrow therapeutic index, caution must be exercised when co-administering voclosporin with digoxin, with appropriate monitoring of digoxin performed as clinically indicated and described in the digoxin product labelling.

OATP1B1/OATP1B3 substrates
The effect of voclosporin on OATP1B1/OATP1B3 substrates (e.g. simvastatin, atorvastatin, pravastatin) has not been studied clinically. However, voclosporin is an OATP1B1/OATP1B3 inhibitor *in-vitro*, and information suggests an increase in the concentration of these substrates is possible. Monitor use of OATP1B1/OATP1B3 substrates when used concomitantly with voclosporin (see "Pharmacokinetics").

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

CYP3A4 substratesl
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.

Based on *in-vitro* studies, voclosporin does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or induce CYP1A2, 2B6, 3A4.

In-vitro data indicate that voclosporin is not a substrate though is an inhibitor of OATP1B1 and OATP1B3. Voclosporin does not inhibit the following transporters at clinically relevant concentrations: BCRP, OAT1, OAT3, OCT2, MATE1 or MATE2.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of Lupkynis in pregnant women. Studies in animals have shown reproductive toxicity in rats and rabbits (see "Preclinical data").
Lupkynis should not be used during pregnancy unless the expected benefit outweighs the potential risk.

Lactation

It is unknown whether voclosporin/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of voclosporin/metabolites in milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lupkynis therapy. This should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Breast-feeding is not recommended for at least 7 days after intake of the final dose.

Fertility

There are no data on the effect of voclosporin on human fertility. Animal studies in rats have shown changes in the male reproductive tract (see "Preclinical data").

Effects on ability to drive and use machines

The influence of voclosporin on the ability to drive and use machines was not investigated.

Undesirable effects

Summary of the safety profile

The safety of voclosporin has been investigated in two pivotal placebo-controlled studies in LN patients with a treatment duration of up to 52 weeks.

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 "Warnings and precautions").

The most frequently reported adverse drug reactions (ADRs) with use of voclosporin are eGFR decreased (19.1%) and hypertension (7.5%). These reactions are responsive to dose reduction. The most frequently reported serious ADRs with the use of voclosporin were infections (1.9%) and hypertension (1.1%).

List of adverse reactions

Adverse drug reactions that occurred in patients receiving the recommended dose of Lupkynis in clinical studies (n = 267) are summarised in Table 3.

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

Table 3: Adverse drug reactions detected in clinical trials

System organ class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infection[1] (24.0%)	Herpes zoster Gastroenteritis Urinary tract infection	
Blood and lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders		Decreased appetite	Hyperkalaemia
Nervous system disorders		Tremor Headache	Seizures
Vascular disorders		Hypertension[2]	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Diarrhoea Abdominal pain[3] Nausea Gingival hyperplasia[4] Dyspepsia	
Skin and subcutaneous tissue disorders		Hypertrichosis[5]	
Renal and urinary disorders	Glomerular filtration rate decreased[6,7] (19.1%)	Acute kidney disease[6] Acute kidney injury[6]	

[1] Includes the following Preferred Terms (PTs): viral upper respiratory tract infection and upper respiratory tract infection bacterial

[2] Includes the following Preferred Terms (PTs): hypertension, blood pressure increased, diastolic blood pressure 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 PT hirsutism

[6] Includes the PT renal impairment

[7] Includes the PT blood creatinine increased

Description of specific adverse reactions and additional information

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. Infections leading to discontinuation of treatment occurred in 2.2% of patients receiving voclosporin and 1.9% of patients receiving placebo; infections leading to dose modification of medicinal product occurred in 13.5% of patients receiving voclosporin and 12.4%

of patients receiving placebo. 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 “Warnings and precautions”).

Renal toxicity
Adverse events suggestive of renal toxicity which occurred at a frequency of ≥ 1% higher in voclosporin compared to placebo were eGFR decreased (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 events were reported in 5.2% of voclosporin patients and 3.4% of placebo patients.

The most common adverse events leading to dose modification (reduction in dose or temporary discontinuation) were eGFR decreases (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 events leading to permanent medicinal product discontinuation were eGFR decreases (voclosporin 3.7%, placebo 1.9%) and renal impairment (voclosporin 1.9%, placebo 1.5%).

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 and led to dose modification in 2.2% of voclosporin patients and to permanent discontinuation of voclosporin in 0.7% of patients. Serious hypertension occurred in 1.9% of voclosporin patients and 0.4% of placebo patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

Experience with overdose is limited. Very few cases of accidental overdose have been reported with voclosporin; symptoms have included tremor and tachycardia. In a drug-drug interaction study in healthy volunteers, in which co-administration of ketoconazole and voclosporin resulted in an 18.6-fold increase in voclosporin exposure, increases in serum creatinine, decreases in serum magnesium and increases in blood pressure were observed.

Treatment

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.

Properties/Effects

ATC code

L04AD03

Immunosuppressants, calcineurin inhibitors

Mechanism of action

Voclosporin is a calcineurin-inhibitor immunosuppressant. 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.

Studies in animal models also support a non-immunological role for calcineurin inhibition in kidney function to stabilise actin cytoskeleton and stress fibres in podocytes leading to increased podocyte integrity in glomeruli.

Pharmacodynamics

Calcineurin inhibition
Concentration-dependent calcineurin inhibition, measured as the percent of maximum calcineurin inhibition, was observed after oral administration of voclosporin twice daily in healthy volunteers. There is little or no lag time between the time to maximum active substance concentration and the time to maximum calcineurin inhibition. Voclosporin inhibits calcineurin in a dose-dependent manner up to a maximum dose of 1.0 mg/kg. At a dose of voclosporin 23.7 mg twice daily, calcineurin inhibition was determined to be 16% at C_{trough} and 58% at C_{max}.

Cardiac Electrophysiology
In a randomized, 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.

The effect of multiple doses of twice daily voclosporin 0.3 mg/kg, 0.5 mg/kg and 1.5 mg/kg on QTc interval was evaluated in a randomised, placebo- and active-controlled (moxifloxacin 400 mg), crossover study in 31 healthy subjects. For the 0.3 mg/kg and 0.5 mg/kg voclosporin dose groups (therapeutic LN dose range), the mean maximum difference from placebo on QTcF interval was 0.8 msec and 2.4 msec, with the upper limit of the one-sided 95% CI of 4.7 msec and 6.2 msec, respectively. At the supra-therapeutic dose of 1.5 mg/kg twice daily, the mean difference from placebo to QTcI interval was 2.8 msec with the upper limit of the one-sided 95% CI of 6.9 msec. 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 negative slope (-0.065344 msec/ng/mL), not statistically different from a slope of 0 ($p = 0.1042$).

Clinical efficacy

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 low dose 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.
Throughout the studies, patients were not allowed to take immunosuppressants (besides MMF and hydroxychloroquine/chloroquine) or modify dose of angiotensin-II receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors.

Safety and efficacy were further investigated in a 2-year continuation study (AURORA 2) in patients that completed the AURORA 1 study.

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) versus placebo (n = 178) over a 52-week treatment period. More patients in the voclosporin arm than the placebo arm achieved the primary endpoint of adjudicated renal response (defined as urine protein to creatinine ratio (UPCR) ≤ 0.5 mg/mg with normal, stable renal function, and presence of sustained, low-dose steroids) at 52 weeks (40.8% vs. 22.5%, OR = 2.65; 95% CI: 1.64, 4.27; P < 0.001).
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 subjects were female (87.7%), of which 81.8% were of childbearing potential.
Most subjects 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.

All pre-specified hierarchical secondary endpoints achieved statistical significance in favour of voclosporin, (see Table 4).

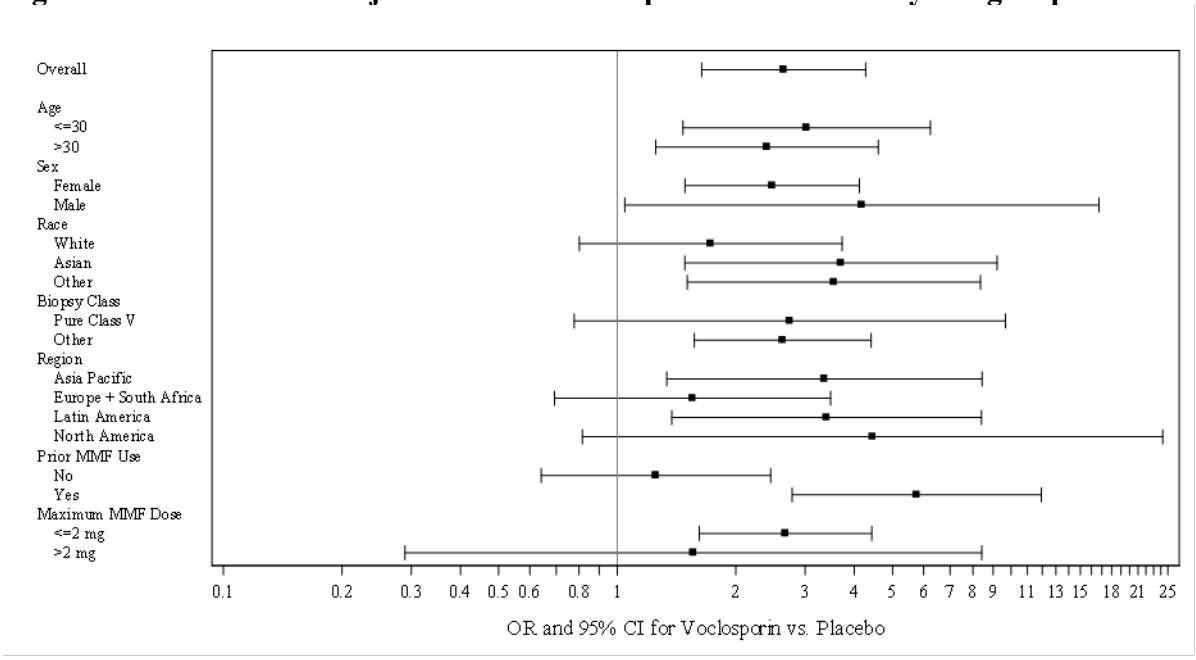
Table 4: AURORA 1 – Summary of hierarchical endpoints

	Voclosporin (n = 179) n (%)	**Placebo (n = 178) n (%)**	**Odds ratio vs. placebo (95% CI)**	**p-value**
Adjudicated renal response at week 52	73 (40.8)	40 (22.5)	2.65 (1.64, 4.27)	< 0.001
Adjudicated 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
Time to UPCR ≤ 0.5 mg/mg	Voclosporin faster than control		2.02 (1.51, 2.70)	< 0.001
Time to 50% reduction in UPCR	Voclosporin faster than control		2.05 (1.62, 2.60)	< 0.001

* Partial renal response defined as a 50% reduction in UPCR.
Notes: CI = Confidence interval; UPCR = Urine protein to creatinine ratio

Results of the covariate analyses by age, sex, race, region, biopsy class, MMF at screening and maximum dose of MMF showed that the odds ratios favoured voclosporin over placebo in all subgroups (Figure 1).

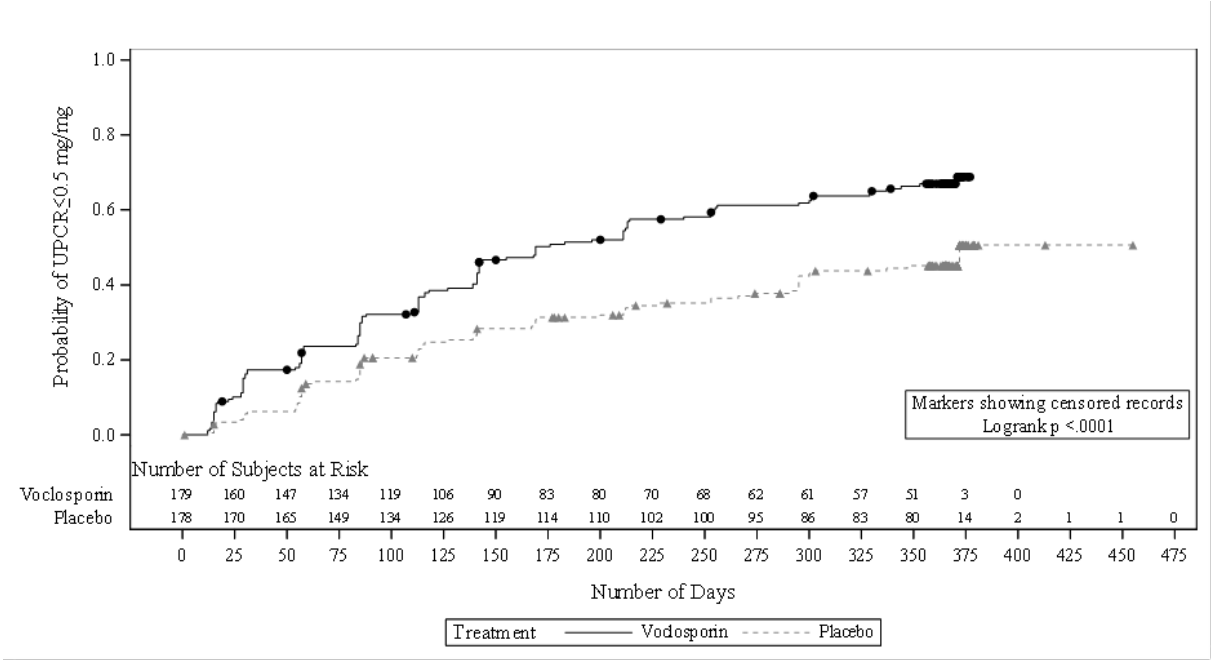
Figure 1: Forest Plot of Adjudicated Renal Response at Week 52 by Subgroup



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).

As seen from the Kaplan-Meier plot (Figure 2), the difference between the two treatments was apparent within the first month of treatment and was sustained throughout the study.

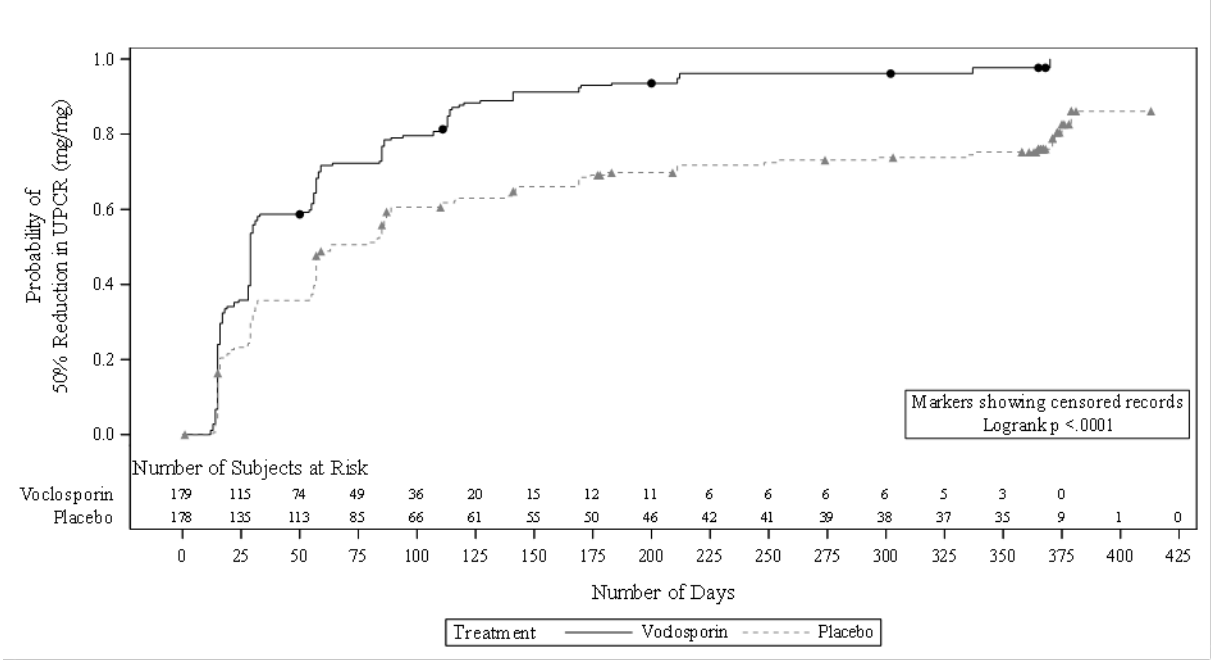
Figure 2: Kaplan-Meier curve of time (days) to UPCR ≤ 0.5 mg/mg



A 50% reduction in UPCR from baseline was achieved by 96.6% of patients treated with voclosporin compared with 75.8% of patients receiving placebo. 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 3).

Figure 3: Kaplan-Meier curve of time (days) to 50% reduction in UPCR from baseline



Phase 3 AURORA 2
The AURORA 2 study was a continuation study in patients that completed the AURORA 1 study. Patients stayed on the same treatment they were receiving at the end of AURORA 1 for a further 2 years.

Voclosporin was well tolerated with no new or unexpected safety signals observed in patients who continued on voclosporin. The incidence of adverse events reduced over time in both arms, and the 3-year safety data of voclosporin in patients with lupus nephritis are not indicative of chronic renal toxicity, neurotoxicity or frequent occurance of malignancies. In addition, mean eGFR was stable over the 3-year treatment period.

The proportion of patients achieving UPCR ≤ 0.5 mg/mg was sustained over the course of the study in both arms. The proportion of patients achieving UPCR ≤ 0.5 mg/mg was greater at all time points in the voclosporin group compared to placebo group.

Pharmacokinetics

Absorption

Following oral administration (voclosporin 23.7 mg twice daily, fasting) 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. Voclosporin is not a substrate of the efflux transporters P-gp or breast cancer resistance protein (BCRP).

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.

Metabolism

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.

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. A greater than dose proportional increase was observed; however, 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.

Kinetics in specific patient groups

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 2.0-fold, respectively (see “Dosage/Administration”). Voclosporin has not been evaluated in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended (see “Warnings and precautions”).

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 (CLCr) 60 mL/min to 89 mL/min as estimated by Cockcroft Gault) and moderate (CLCr 30 mL/min to 59 mL/min) renal impairment

compared to volunteers with normal renal function (CLCr ≥ 90 mL/min). After a single dose of voclosporin in volunteers with severe renal impairment (CLCr < 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 “Dosage/Administration”).

Age, sex, race and body weight

A population pharmacokinetic analysis assessing the effects of age (18 to 66 years), sex, race and body weight (37 to 133 kg) did not suggest any clinically significant impact of these covariates on voclosporin exposures.

Preclinical data

Long-term toxicity
Repeated-dose animal studies have shown cataracts and neurohistological findings of gliosis and perivascular infiltrates in the brain and spinal cord in rats, but not in dogs or monkeys.
In a 39-week oral toxicology study in cynomolgus monkeys, malignant lymphomas were observed at exposures 4 times the AUC at the recommended clinical dose of 23.7 mg twice daily.

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

Carcinogenicity
In a 2-year mouse carcinogenicity study with oral voclosporin, an increased incidence of malignant lymphoma was observed at exposures 5.4-fold the AUC at the recommended clinical dose of 23.7 mg twice daily. In a 2-year rat carcinogenicity study with oral voclosporin, there was no evidence of carcinogenicity. However, the exposure was lower than the human exposure at the proposed clinical dose.
In a 39-week oral toxicology study in cynomolgus monkeys, malignant lymphomas were observed at exposures 4 times up to 7 times the AUC at the recommended clinical dose of 23.7 mg twice daily.

Reproductive toxicity
In a rat fertility study with a 50:50 mixture of voclosporin and its cis-isomer at a dose of 25 mg/kg/day, no effects on mating and fertility parameters and on sperm count and motility were observed at exposures, which corresponded to 9 to 16 times the AUC at the recommended clinical dose of 23.7 mg twice daily.

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 observed at doses that were associated with maternal toxicity (at exposures15-times and 1-times the AUC at the recommended clinical dose of 23.7mg twice daily). 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.

In a pre- and post-natal developmental study in rats, maternal toxicity at a dose of 25 mg/kg/day voclosporin (i.e at exposure 12 times the AUC at the recommended clinical dose of 23.7mg twice daily) a maternal toxicity caused delay in parturition (dystocia) was observed that resulted in reductions in the mean number of pups burn and surviving pups per litter. No adverse effects were observed in the dams or their offspring at exposures 3 times the AUC at the recommended clinical dose of 23.7 mg twice daily.

Drug-derived radioactivity was rapidly distributed to milk following the oral administration of [14C]-voclosporin to lactating rats.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 25°C.
Store in the original packaging (blister) in order to protect from moisture.
Keep out of reach of children.

Authorisation number

68697 (Swissmedic)

Packs

Lupkynis 7.9 mg soft capsules packed in blisters. One carton contains 180 soft capsules. [B]

Marketing authorisation holder

Otsuka Pharmaceutical (Switzerland) GmbH, Opfikon

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August 2022