Summary of risk management plan (RMP) for Lupkynis (voclosporin)

Version 1.0 Switzerland

Marketing Authorisation Holder:
Otsuka Pharmaceutical (Switzerland) GmbH

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Lupkynis is a concise document and does not claim to be exhaustive.

Please note that the reference document which is valid and relevant for the effective and safe use of "name of the medicinal product" in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Otsuka Pharmaceutical (Switzerland) GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Lupkynis.

I. The medicine and what it is used for

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 class III/V and IV/V) lupus nephritis (LN) (see Product Information for the full indication). It contains voclosporin as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lupkynis, together with measures to minimise such risks and the proposed studies for learning more about Lupkynis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lupkynis is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lupkynis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lupkynis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	▪ Serious infections including opportunistic infections ▪ Nephrotoxicity (acute and chronic)
Important potential risks	▪ Major adverse cardiovascular events (MACEs) ▪ Neurotoxicity ▪ Malignancies (including lymphomas) associated with long term use
Missing information	▪ Use in pregnancy

II.B Summary of important risks

Important identified risk: Serious infections including opportunistic infections	
Evidence for linking the risk to the medicine	**Clinical trials**: The incidence of serious infections including opportunistic infections was marginally higher in the voclosporin group compared to the placebo group in the pooled LN population, In AURORA 2, the incidence was lower and comparable, between the two treatment arms indicating that the frequency of serious infection including opportunistic infections was higher in the first 12 months of treatment. **Class effect**: Like other immunosuppressants, CNIs predispose patients to the development of a variety of bacterial, fungal, parasitic, and viral infections, including opportunistic pathogens.
Risk factors and risk groups	Patients who are using immunosuppressive treatment of any kind have an increased risk of opportunistic infection.
Risk minimisation measures	**Routine risk minimisation measures**: Product Information: Warnings and Precautions, Undesirable Effects Information for Patients Information for Patients Legal status: Prescription only medicine **Additional risk minimisation measures**: None

Important identified risk: Nephrotoxicity (acute and chronic)	
Evidence for linking the risk to the medicine	**Non-clinical:** Toxicity studies in rats showed renal effects including increases in blood urea nitrogen and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralization. **Clinical trials**: There has been no indication of true voclosporin-related nephrotoxicity in the clinical development program with treatment up to three years. LN causes a loss of renal function which is manifest by a decreasing eGFR and an increase in UPCR. In addition, voclosporin has a haemodynamic effect leading to a small decrease in eGFR which is reversible on stopping treatment. Data from the long-term AURORA 2 trial supports the lack of nephrotoxicity of voclosporin over a 3-year period. An assessment of eGFR levels over time from the start of AURORA 2 shows that mean eGFR levels were generally stable from Month 12 to Month 27 after which point the mean eGFR levels in the voclosporin group increased while those in the placebo group decreased, potentially reflecting a worsening of renal function relating to disease progression in some placebo subjects. **Class effect**: Renal toxicity is a known effect of CNIs seen most frequently in kidney transplant recipients.
Risk factors and risk groups	Patients with LN by definition have renal disease. A cross-sectional observational study based on data from the Spanish Registry of Glomerulonephritis for the years 1994–2009 showed that risk factors associated with renal failure in patients with LN were older age, male gender, intensity of proteinuria, and presence of hypertension.
Risk minimisation measures	**Routine risk minimisation measures**: Product Information: Dosage/Administration, Warnings and Precautions, Undesirable Effects Information for Patients Legal status: Prescription only medicine

	Additional risk minimisation measures: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis AURORA 2 biopsy sub-study

Important potential risk: MACEs	
Evidence for linking the risk to the medicine	**Clinical trials**: The number of subjects with MACE TEAEs or treatment-emergent fatal cardiovascular events was low across both treatment groups in the pooled LN population: 5 subjects in the placebo group had a TEAE meeting the MACE criteria compared with 4 subjects in the voclosporin group. An analysis of exposure adjusted incidence rates (EAIRs) of TEAEs did not show any statistically significant differences between treatment groups and the overall EAIR was higher in the placebo group compared with the voclosporin group. In AURORA 2 there were no MACE TEAEs in the voclosporin group and one MACE TEAE of pulmonary embolism in the placebo group. Hypertension is a risk factor for MACE. In the pooled LN population, hypertension, including treatment related hypertension, occurred more frequently in the voclosporin group compared to placebo. In AURORA 2, the frequency was lower and comparable between the two groups indicating that the frequency of hypertension was higher in the first 12 months of treatment. The majority of events in the voclosporin and placebo groups in the pooled LN and AURORA 2 populations were mild or moderate. **Class effect**: As a class, CNIs induce hypertension which is a risk factor for MACE.
Risk factors and risk groups	Patients with LN are a population at greater risk of experiencing cardiovascular AEs such as MACEs due to inflammation, elevated blood lipids, antiphospholipid syndrome. Additionally, hypertension, obesity, smoking, diabetes, family history and lack of exercise are risk factors for MACEs.
Risk minimisation measures	**Routine risk minimisation measures**: (hypertension) Product Information: Warnings and Precautions, Undesirable Effects Information for Patients Legal status: Prescription only medicine **Additional risk minimisation measures**: None

Important potential risk: Neurotoxicity	
Evidence for linking the risk to the medicine	**Clinical trials**: In the pooled LN population, TEAEs in the Nervous System Disorders SOC occurred at a higher rate in the voclosporin group than in the placebo group. However, the Nervous System Disorders SOC contains some terms which are not indicative of neurotoxicity. Six preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, tremor, post-herpetic neuralgia, paraesthesia, hypoaesthesia and seizure); the remaining events occurred either at a lower incidence in voclosporin compared with placebo or occurred in only 1 or 2 subjects in any treatment group. In AURORA 2, Nervous System Disorder TEAEs occurred more frequently in the

	voclosporin treated patients compared to the placebo group. Three preferred terms occurred with an incidence in the voclosporin group ≥ 1% higher than placebo (headache, hypoaesthesia and dizziness). **Class effect**: CNIs have been associated with hypertensive encephalopathy and posterior reversible encephalopathy syndrome (PRES) (Farouk et al 2020).
Risk factors and risk groups	There are no clear risk factors for neurotoxicity. However, the prevalence of PRES among patients with SLE ranges from 0.7% to 1.4% with recurrence in up to 15% of cases. Risk factors include SLE activity, hypertension, haematologic and renal disease (Valdez-Lopez 2021). Female gender, hypertension and exposure to immunosuppressive therapy and heroin consumption have been postulated as additional risk factors (Ansari 2021).
Risk minimisation measures	**Routine risk minimisation measures**: Product Information: Warnings and Precautions, Undesirable Effects Information for Patients Legal status: Prescription only medicine **Additional risk minimisation measures**: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Important potential risk: Malignancies (including lymphomas) associated with long term use	
Evidence for linking the risk to the medicine	**Non-clinical:** Daily oral administration of voclosporin for 60 to 89 weeks to mice was associated with higher incidences of malignant lymphoma. **Clinical trials**: There has been no indication of malignancy events related to voclosporin in the clinical development programme over the three year period. **Class effect**: Like other immunosuppressants, CNIs increase the risk of developing lymphomas and other malignancies, particularly those of the skin.
Risk factors and risk groups	Long-term immunosuppression.
Risk minimisation measures	**Routine risk minimisation measures**: Product Information: Warnings and Precautions, Undesirable Effects, Preclinical Data Information for Patients Legal status: Prescription only medicine **Additional risk minimisation measures**: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis

Missing information: Use in pregnancy	
Risk minimisation measures	**Routine risk minimisation measures**: Product Information: Pregnancy/Lactation, Preclinical Data Information for Patients Legal status: Prescription only medicine **Additional risk minimisation measures**: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lupkynis.

II.C.2 Other studies in post-authorisation development plan

1.Study short name and title: Kidney biopsy sub-study

Rationale and Study Objectives

The kidney biopsy is accepted as the gold standard for the diagnosis of glomerular diseases, and biopsy findings are used to classify and subgroup the forms of lupus nephritis (LN). Proteinuria is well accepted in regular clinical practice as a marker of treatment response and overall prognosis in LN. However, there is some data to suggest that renal biopsy provides additional information on renal status during LN treatment both via histology and more recent examination of renal protein and micro-RNA expression. Therefore, within the confines of a clinical trial and to provide more complete information on treatment effect this renal biopsy sub-study will assess renal histology and transcriptomics (proteomics may also be assessed if sufficient samples are available).

The diagnosis of active LN relies on both clinical and histologic findings, with the goal of LN therapy being the achievement of a clinical response, assessed mainly as a reduction in proteinuria and stabilization or improvement in kidney function. However, there is poor correlation between clinical findings and renal histology and little progress has been made in using the kidney biopsy to predict treatment response.

2.Study short name and title: An observational PASS in EU to further characterise and quantify long-term safety profile of Lupkynis.

Rationale and study objectives

In the EU, Lupkynis is anticipated to be 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). The Estimated prevalence of LN ranged from 0.63 to 2.28 per 10,000 persons. The Risk

Management Plan for Lupkynis includes malignancy, neurotoxicity, and chronic nephrotoxicity as Important Potential Risks. The purpose of this PASS study is to assess the occurrence of these events in patients treated with Lupkynis in the real-world setting.