NCPE Assessment

Technical Summary

Voclosporin (Lupyknis®)

HTA ID 23003

December 2024

Applicant: Otsuka Pharmaceuticals UK Ltd

Voclosporin 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

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of voclosporin (Lupkynis®).

Following assessment of the Applicant's submission, the NCPE recommends that voclosporin (Lupkynis®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Otsuka Pharmaceuticals UK Ltd) Health Technology Assessment of voclosporin (Lupkynis®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In September 2023, Otsuka Pharmaceuticals UK Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of voclosporin (Lupkynis®) in combination with mycophenolate mofetil (MMF) for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN). Otsuka Pharmaceuticals UK Ltd is seeking reimbursement of voclosporin on the High Tech Drug Arrangement. Voclosporin received its Marketing Authorisation on the 15th September 2022.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which primarily affects women between the ages of 20 and 40 years. LN is a complication of SLE, causing inflammation in connective tissues and affecting glomeruli cells in the kidneys. LN severity is classified into LN class I to VI, by kidney biopsy according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system. Patients in classes III, IV, and V with active disease are treated with immunosuppressive therapy. Historically, induction therapy with immunosuppressive regimens is given with the aim of achieving complete or partial remission. Maintenance therapy is then continued with the aim of completing remission and preventing renal flares (relapses). In line with international treatment guidelines a minimum of three years treatment is given. If LN is left untreated, patients will progress through stages of chronic kidney disease (CKD). It is estimated that 10% to 30% of patients with LN will develop end-stage renal disease and will require dialysis or kidney transplants to survive. The prevalence of SLE and chances of developing LN vary between different regions of the world and across different races and ethnicities.

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. The recommended dose of voclosporin is 23.7 mg (three 7.9 mg soft capsules), twice daily. The product licence does not make an explicit recommendation on treatment duration.

The Applicant considers the relevant comparators to be MMF alone, low-dose cyclophosphamide (L-CYC), high-dose cyclophosphamide (H-CYC), azathioprine (AZA), rituximab in combination with MMF (RTX + MMF), tacrolimus in combination with MMF (TAC + MMF) and tacrolimus monotherapy (TAC alone). Based on clinical opinion, the Review Group consider MMF alone and TAC + MMF to be the most relevant comparators for the decision problem.

1. Comparative effectiveness of voclosporin

AURORA 1 was a multicentre, double-blind, placebo controlled randomised trial conducted across North and Latin America, Europe, South Africa and Asia. Eligible participants had a diagnosis of SLE with active LN (by kidney biopsy), and confirmation of class III, IV, V (alone or in combination with class III or IV) LN with a urine protein creatine ratio (UPCR) of ≥1.5 mg/mg for class III and IV LN or ≥ 2 mg/mg if pure class V). A key exclusion criterion was an estimated glomerular filtration rate (eGFR) of ≤ 45 ml/min/1.73m^2.

All participants were on a background therapy of MMF at a dose of 1000 mg twice daily, and rapidly tapered low-dose corticosteroids. Participants were randomly assigned (1:1) to voclosporin, at a dose of 23.7mg twice daily (n=179), or placebo (n=178). Randomisation was stratified by biopsy class, MMF use at the time of screening, and region. The primary endpoint was complete renal response (CRR) at 52 weeks adjudicated by a blinded Clinical Endpoints Committee. CRR was defined as a composite of (i) UPCR of ≤0.5 mg/mg, (ii) eGFR of ≥60 ml/min/1.73 m^2 or no confirmed eGFR decrease of >20% from baseline, (iii) no rescue medication, (iv) and no more than 10 mg prednisone equivalent per day for three or more consecutive days or for seven or more days in total during Weeks 44 to 52. Key secondary endpoints included partial renal response (PRR) (defined as ≥ 50% reduction in UPCR from baseline) at Weeks 24 and Weeks 52. Participants who completed 52 weeks of study drug treatment in AURORA 1 could continue their double-blinded treatment of voclosporin or placebo, in combination with MMF and low-dose corticosteroids for a further 24 months as part of the AURORA 2 continuation study.

Overall, 309 participants (86.6%) completed AURORA 1, with more participants in the

voclosporin + MMF arm (162 of 179 [90.5%]) than the placebo + MMF arm (147 of 178 [82.6%]) reaching Week 52. Patient characteristics were generally 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 %). Most patients were White (36.1%) or Asian (30.5%), and approximately one third of the study population was Hispanic or Latino. The mean and median UPCR was > 3 mg/mg at baseline and mean and median eGFR values were > 90 mL/min/1.73 m² (range 25 to 136 mL/min/1.73m²). Most patients (98%) had received treatment for LN in the past, with approximately 55% of patients on MMF at screening.

More patients in the voclosporin + MMF arm than the placebo + MMF arm achieved the primary endpoint of CRR at Week 52 (41% versus 23%, odds ratio 2.65, 95% confidence interval (CI) 1.64 to 4.27, p<0.001). While the composite primary endpoint was statistically significant, the difference in favour of voclosporin + MMF versus placebo + MMF was driven by the difference in one component alone (UPCR ≤0.5mg/mg). Statistically significant improvements in the key secondary outcomes of PRR at Weeks 24 and 52 were also demonstrated.

Of the 357 participants enrolled in AURORA 1, a total of 216 participants (60.5%) continued to receive blinded treatment in AURORA 2: including 116 of 179 (64.8%) participants from the voclosporin +MMF arm and 100 of 178 (56.2%) participants from the placebo + MMF arm. The proportion of AURORA 2 patients in CRR at Month 36 was 51% (59 of 116) in the voclosporin arm and 39% (39 of 100) in the placebo arm.

The Review Group note the use of surrogate endpoints (CRR and PRR) for CKD progression in the AURORA trials. While evidence from clinical trials and observational studies indicates that patients with LN achieving CRR have better long-term CKD outcomes (individual-level surrogacy), this does not necessarily imply that the increased rate of CRR with voclosporin will lead to improved long-term CKD outcomes (trial-level surrogacy has not been demonstrated). Another limitation is that AURORA 2 does not offer a randomised comparison, and is subject to a considerable risk of confounding, selection and attrition bias. Therefore, the higher rates of CRR and PRR observed in the voclosporin + MMF arm of AURORA 2 do not necessarily represent causal effects of voclosporin + MMF treatment.

In the absence of direct comparative evidence, the Applicant conducted a network meta-analysis (NMA) to inform the comparison of voclosporin with the other comparators; L-CYC, H-CYC, AZA, RTX + MMF, TAC + MMF and TAC alone.

The NMA is extremely limited due to substantial heterogeneity between the included trials in terms of study populations, outcome definitions, baseline characteristics and dosing of interventions. Many of the included studies were conducted in exclusively Asian populations, therefore, generalisability to the target population in Ireland is unclear. Many studies in evidence networks enrolled small sample sizes, and/or were of uncertain or poor methodological quality leading to statistical imprecision and risk of bias in the treatment effects obtained from the NMA. Finally, treatment effects on the outcome of partial response lack interpretability as a positive or negative outcome. Therefore, the Review Group do not consider the results of the NMA to provide reliable estimates of comparative effectiveness.

2. Safety of **voclosporin**

In AURORA 1, the most frequently reported adverse reactions with use of voclosporin + MMF were decreased eGFR (26.2%) and hypertension (19.1%). The most frequently reported serious adverse reactions with use of voclosporin + MMF were infections (10.1%), acute kidney injury (3%) and hypertension (1.9%). The overall incidence of infections was 62.2% in the voclosporin MMF arm and 54.9% in the placebo arm. Adverse reactions suggestive of renal toxicity which occurred at a higher frequency with voclosporin + MMF compared with placebo + MMF were decreased eGFR (26.2% versus 9.4%), renal impairment (5.6% versus 2.6%), acute kidney injury (3.4% versus 0.8%), and hyperkalaemia (1.9% versus 0.8%). In AURORA 2, 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 European Public Assessment Report highlights that the most important safety concern for voclosporin is nephrotoxicity. This should be handled by regular monitoring of eGFR levels and dose adjustments or treatment discontinuation if eGFR is decreased.

3. Cost effectiveness of **voclosporin**

Pairwise comparisons of voclosporin to each of its comparators were provided. A maximum

treatment duration of 36 months was assumed in all treatment arms.

Methods

A cohort state transition Markov model was submitted by the Applicant. The CEM included health states according to LN-related stages of CKD (stages 1-3a, stages 3b-4 and CKD stage 5), and Death. Patients with CKD stages 1-3a or CKD stages 3b-4, can transition between various response sub-states (Complete Response, Partial Response or Active Disease). Patients in CKD 5 stage, can transition between dialysis and kidney transplant. All patients enter the model in the Active Disease CKD 1–3a health state. CKD progression cannot occur from Complete Response or Partial Response although the risk of relapse to Active Disease is higher in Partial Response than Complete Response. Transition to Death can occur from any health state.

The model structure relies on the validity of complete response and partial response as surrogates for preventing progression to CKD 3b-4 and onwards to CKD stage 5, and the associated impacts on mortality, morbidity and quality of life. Clinical opinion suggests that this assumption may be reasonable for patients with complete response but less reasonable for patients with partial response. As previously discussed, trial-level surrogacy has not been established. Another key limitation of the model structure is that subsequent induction treatments are not linked to the occurrence of renal flares.

In the voclosporin + MMF arm and the MMF alone arm, health state transitions between Active Disease, Partial Response, and Complete Response for patients with CKD 1-3a were estimated based on individual patient-level data from AURORA 1 and AURORA 2 trials. AURORA 1 data were used to inform the transitions between baseline to 6 months and 6 months to 12 months, while AURORA 2 data were used to inform the transitions from 12 months onwards. After 36 months, a post-follow-up transition matrix, based on the final year of AURORA 2, was used to estimate long-term transitions following treatment discontinuation. Transition probabilities for other treatments in CKD 1-3a were calculated by applying the odds ratios of achieving complete response and partial response for each treatment versus MMF obtained from the NMA, to the probabilities of transitioning from Active Disease to Complete Response and Partial Response respectively for the MMF alone arm of the AURORA trials. Transitions from Active Disease CKD 1-3a to Active Disease CKD

3b-4 and all other transitions outside the CKD 1-3a health states were based on either clinical opinion, literature sources or Applicant assumptions. Treatment independent utility values for CKD 1-3a health states were derived from SF-36 utilities collected in AURORA 1 and AURORA 2 mapped to EQ-5D-3L. Literature sources were used to inform utility values for the remaining health states.

The Review Group had a number of concerns with the Applicant base case including

- Rates of progression from CKD 1-3a and CKD 3b-4 are based on clinical opinion and are highly uncertain.
- The use of AURORA 2 data to predict long-term renal response and relapse probabilities may not model the long-term trajectory of LN appropriately.
- The model assumes a lifetime reduced risk of relapse from Complete Response to Active Disease after treatment discontinuation, for which there is no supporting evidence.
- The high level of censoring in AURORA 1 and AURORA 2 has the potential to bias the cost-effectiveness results in an unknown direction.
- Transition probabilities for comparators other than MMF alone are highly uncertain due to the limitations of the NMA.

The Review Group addressed a number of limitations in the Applicant's cost-effectiveness analysis, through changes in the NCPE adjusted base case. These included basing long-term transition probabilities on the entire AURORA 2 study and only allowing a reduced risk of relapse from Complete Response to Active Disease for five years following treatment discontinuation.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively. For all comparisons, the results of cost-effectiveness analysis depend on the validity of complete response and partial response as surrogate outcomes for delaying and/or preventing long-term CKD stage progression, which is a major source of uncertainty. In addition, reliable estimation of incremental cost-effectiveness for comparators other than MMF alone is not possible due to the limitations of the NMA.

Table 1: NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Voclosporin + MMF	81,798	12.46	-	-	-
MMF alone	56,490	12.03	25,308	0.433	58,489
Other comparators from the NMA[b]					
L-CYC	56,330	11.82	25,468	0.645	39,481
H-CYC	56,387	11.75	25,412	0.716	35,479
AZA	53,238	12.00	28,560	0.466	61,281
RTX + MMF	63,523	12.31	18,276	0.149	122,632
TAC + MMF	60,138	11.86	21,660	0.601	36,043
TAC alone	60,866	12.05	20,933	0.410	51,098

AZA: azathioprine; H-CYC: high-dose cyclophosphamide; ICER: incremental cost-effectiveness ratio; L-CYC: high-dose cyclophosphamide; MMF: mycophenolate mofetil; NMA: network meta-analysis; QALY: quality-adjusted life year; RTX: rituximab; TAC: tacrolimus

[a] Corresponding probabilistic ICER using 1,000 iterations: €57,260/QALY (MMF alone); €36,747/QALY (L-CYC); €34,794/QALY (H-CYC), €57,901/QALY (AZA); €126,769 (RTX + MMF); €33,740/QALY (TAC + MMF); €46,342/QALY (TAC). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes

[b] Reliable estimation of NMA comparator ICERs are not possible due to the limitations of the NMA

Table 2: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Voclosporin + MMF	94,330	12.60	-	-	-
MMF alone	73,076	12.09	21,254	0.502	42,302
Other comparators from the NMA[b]					
L-CYC	74,105	11.86	20,225	0.740	27,329
H-CYC	74,290	11.80	20,040	0.799	25,086
AZA	70,187	12.06	24,143	0.537	44,960
RTX + MMF	77,781	12.37	16,549	0.227	72,999
TAC + MMF	76,026	11.95	18,304	0.650	28,173
TAC alone	77,196	12.11	17,134	0.482	35,539

AZA: azathioprine; H-CYC: high-dose cyclophosphamide; ICER: incremental cost-effectiveness ratio; L-CYC: high-dose cyclophosphamide; MMF: mycophenolate mofetil; NMA: network meta-analysis; QALY: quality-adjusted life year; RTX: rituximab; TAC: tacrolimus

[a] Corresponding probabilistic ICER using 1,000 iterations: €44,370/QALY (MMF alone); €27,751/QALY (L-CYC); €26,331/QALY (H-CYC); €45,123 (AZA); €26,098 (TAC + MMF); €35,172 (TAC alone). Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes

[b] Reliable estimation of NMA comparator ICERs are not possible due to the limitations of the NMA

Sensitivity analysis

Under the NCPE adjusted base case the probability of cost-effectiveness for the comparison of voclosporin + MMF versus MMF alone at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 0% and 7.7%, respectively. Under the Applicant base case the probability of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 0.3% and 34.6%, respectively. The model structure did not allow for the relationship between the surrogate outcomes of complete and partial response and the main patient-relevant outcome of CKD progression to be robustly investigated via

sensitivity analysis, therefore the probabilities presented do not capture the full extent of uncertainty in the model.

In the case of the comparison with MMF alone, a discount of 31.0% and 72.8% in the price to wholesaler of voclosporin (inclusive of Framework Agreement rebate) would be required for voclosporin + MMF to be considered cost-effective at a willingness-to-pay threshold of €45,000 per QALY and €20,000 per QALY, respectively.

4. Budget impact of voclosporin

The price to wholesaler for one pack of voclosporin 7.9mg soft capsules (pack size of 180), is €1,135.38. Assuming a relative dose intensity in line with AURORA 1, the treatment cost per patient per year is €14,192 (including pharmacy fees and applying a Framework Agreement rebate of 8.5%).

Based on a market share estimate of 1.3% in Year 1 increasing to 10% in Year 5, the Applicant predicts 16 patients will receive voclosporin in Year 1 increasing to 96 in Year 5. Assuming that these patients remain on voclosporin for three years, the Applicant estimates the five-year cumulative gross and net drug-budget impact for voclosporin + MMF to be €5.85 million and €5.49 million, respectively. The Review Group consider the market share estimates and consequently the predicted patient numbers to be unrealistically low considering this is the first licensed treatment for LN.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that voclosporin (Lupkynis®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.