SMC2570

voclosporin soft capsule (Lupkynis®)

Otsuka Pharmaceutical (UK) Ltd

08 September 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

voclosporin (Lupkynis®) is accepted for use within NHSScotland.

Indication under review: 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.

Addition of voclosporin to mycophenolate mofetil significantly improved renal response rate in adults with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Voclosporin is a calcineurin inhibitor. Its immunosuppressant effects result from inhibition of lymphocyte proliferation, T-cell cytokine production and expression of T-cell activation surface antigens. It is given in combination with the immunosuppressant, mycophenolate mofetil, which inhibits inosine monophosphate dehydrogenase to have a cytostatic effect on lymphocytes. Both medicines are administered orally. The recommended dose of voclosporin is 23.7mg twice daily. Physicians should evaluate the efficacy of treatment at a time point of at least 24 weeks and make an appropriate risk-benefit analysis for continuation of therapy.[1,2]

1.2. Disease background

Systemic Lupus Erythematosus (SLE) is a chronic, relapsing-remitting, multi-system, auto-immune disease, with accumulated damage and increased risk of premature death. It primarily affects women between the ages of 20 and 40 years. The clinical features of acute disease are mostly due to inflammatory processes triggered by the formation of immune complexes.[3] In the most common serious manifestation, lupus nephritis, immune complexes cause renal damage. It is estimated that 10% to 30% of patients with lupus nephritis develop end-stage renal disease, which is associated with a 26-fold increase in mortality compared with the general population. There is evidence that Black and Hispanic patients with SLE develop lupus nephritis earlier and have worse outcomes than White patients with SLE, including death and end-stage renal disease. Lupus nephritis is categorised in to classes (I to VI) based on renal (glomerular) lesions.[4,5]

1.3. Treatment pathway and relevant comparators

For the initial management of Class III, IV or V lupus nephritis the British Society of Rheumatology (BSR) guideline recommends mycophenolate mofetil (or cyclophosphamide) in combination with glucocorticoids (three intravenous methylprednisolone doses then oral prednisone 0.5mg/kg/day for four weeks, reducing to ≤10mg/day by four to six months). In pure class V nephritis with nephrotic-range proteinuria, cyclophosphamide, calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are alternatives to mycophenolate mofetil for non-responders. After improvement with initial treatment, immunosuppression should continue with either mycophenolate mofetil at lower doses or azathioprine for at least three years, in combination with low-dose prednisone. Gradual drug withdrawal, glucocorticoids first, can then be attempted.[3]

The immunosuppressant, belimumab (a monoclonal antibody to soluble human B Lymphocyte Stimulator protein), has been accepted by SMC for restricted use in active SLE (SMC2477) but, in the absence of a submission, it is not accepted for use in combination with background immunosuppressive therapies for active lupus nephritis (SMC2483).

1.4. Category for decision-making process (if appropriate)

Eligibility for a PACE meeting
Voclosporin meets orphan equivalent criteria in this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the AURORA-1 and AURA-LV studies detailed in Table 2.1 below and from AURORA-2, which included patients from AURORA-1 who wished to continue their randomised treatment for a further 24 months. The primary objective in AURORA-2 was safety. However, a key secondary outcome was renal response, assessed using the same criteria as in AURORA 1.[5-7]

Table 2.1. Overview of relevant studies.[5-7]

Criteria	AURORA-1	AURA-LV
Study design	Double-blind, phase III	Double-blind, phase II
Eligible patients	Adults with SLE and class III, IV-S, IV-G or V LN; require immunosuppressant and glucocorticoids for active LN	Adults with SLE and class III, IV-S, IV-G or V LN; require immunosuppressant and glucocorticoids for active LN
Treatments	Twice daily oral voclosporin 23.7mg or placebo. Mycophenolate mofetil 1g twice daily and tapered corticosteroid given to all patients.	Twice daily oral voclosporin 23.7mg or 39.5mg or placebo. Mycophenolate mofetil 1g twice daily and tapered corticosteroid given to all patients.
Randomisation	Stratified by LN class (pure class V versus others), mycophenolate mofetil use at screening and region	Stratified by LN class (pure class V versus others) and mycophenolate mofetil use at screening
Primary outcome	Complete renal response at Week 52, defined as a composite of: UPCR ≤0.5mg/mg; eGFR≥60ml/min/1.73m^2 or no confirmed decrease ≥20%; no rescue medication; and prednisolone ≤10mg daily for ≥3 days or for ≥7 days in total during Weeks 44 to 52.	Complete renal response at Week 24, defined as a composite of: UPCR ≤0.5mg/mg; eGFR≥60ml/min/1.73m^2 or no confirmed decrease ≥20%; no rescue medication; and prednisolone ≤10mg daily for ≥3 days or for ≥7 days in total during Weeks 16 to 24.
Secondary outcomes	Hierarchical order: time to UPCR ≤0.5mg/mg; partial renal response at Week 24; partial renal response at Week 52; time to ≥50% reduction in UPCR; complete renal response at Week 24	Complete renal response at Week 48; partial response at Week 24; time to responses; duration of responses; and several others.
Statistical analysis	Hierarchical testing of primary then secondary in order above.	No adjustment for multiplicity.

eGFR = estimated glomerular filtration rate; LN = lupus nephritis; SLE = systemic lupus erythematous; UPCR = urine protein creatinine ratio.

In the AURORA-1 study, the primary outcome, complete renal response at Week 52, and all the secondary outcomes in the hierarchical testing strategy significantly improved with voclosporin compared with placebo. In the AURA-LV study the primary outcome, complete renal response at Week 24, was achieved by significantly more patients in the voclosporin 23.7mg group, but not the voclosporin 39.5mg group, compared with placebo.[5-7] The results of the AURORA-1 study and the licensed dose (23.7mg) in the AURA-LV study are detailed Table 2.2 below.

Table 2.2: Results of AURORA-1 and AURA-LV studies.[5-7]

	Voclosporin	Placebo	Odd ratio (OR) or Hazard ratio (HR) (95% CI)
AURORA-1	**n=179**	**Nn=178**	
Renal response at week 52[a]	73 (41%)	40 (22%)	OR 2.65 (1.64 to 4.27)[b]
Median time to UPCR ≤0.5mg/mg, days	169	372	HR 2.02 (1.51 to 2.70)[b]
Partial renal response at week 24	126 (70%)	89 (50%)	OR 2.43 (1.56 to 3.79)[b]
Partial renal response at week 52	125 (70%)	92 (52%)	OR 2.26 (1.45 to 3.51)[b]
Median time to ≥50% reduction UPCR, days	29	63	HR 2.05 (1.62 to 2.60)[b]
Renal response at week 24	58 (32%)	35 (20%)	OR 2.23 (1.34 to 3.72)[c]
AURA-LV	**n=89**	**n=88**	
Renal response at week 24[a]	29 (33%)	17 (19%)	OR 2.03 (1.01 to 4.05)[d]
Renal response at week 48	44 (49%)	21 (24%)	OR 3.21 (1.68 to 6.13)

a = primary outcome; b = p-value <0.001; c = p-value 0.002; d =p-value 0.046; CI = confidence interval; HR = hazard ratio; OR = odds ratio; UPCR = urine protein creatinine ratio.

A pre-specified analysis by mycophenolate mofetil use at screening suggests heterogeneity. In the subgroup taking this medicine at screening (55% of the study population), the Week 52 renal response rate odds ratio (OR) was 5.8 (95% confidence interval [CI]: 2.8 to 11.9). However, in the subgroup of patients (45% of the study population) who were not taking mycophenolate mofetil at screening, the Week 52 renal response rate OR was lower: 1.3 (95% CI: 0.6 to 2.5).[6,8]

The AURORA-2 study included 65% (116/179) and 56% (100/178) of patients from the AURORA-1 voclosporin and placebo groups, respectively. Renal response rates were maintained up to 36 months. In this group of patients, an adequate renal response (sustained urine protein creatinine ratio [UPCR] ≤0.7mg/mg) was achieved by 87% (101/116) and 73% (73/100), respectively. The proportions who subsequently had a renal flare appear similar with voclosporin and placebo: 24% (24/101) and 26% (19/73), respectively, with an OR of 0.85 (95% CI: 0.42 to 1.73). Severe renal flares were noted in five and four patients, in the respective groups.[5]

2.2. Health-related quality of life outcomes

In AURORA-1, there were improvements in the health-related quality of life assessment, short-form 36 (SF-36) and the health-related domains of Lupus patient-reported outcomes (LupusPRO) in both treatment groups with no substantial differences between them.[5]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

A Bayesian network meta-analysis (NMA) compared the voclosporin plus mycophenolate mofetil regimen with a number of comparators as detailed in Table 2.4 below. The results were applied to the economic analysis.

Table 2.4: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis.
Population	Adults with class III, IV or V active lupus nephritis.
Comparators	Comparator regimens generally included corticosteroids in combination with the immunosuppressant: mycophenolate mofetil; cyclophosphamide; azathioprine; tacrolimus; tacrolimus plus mycophenolate mofetil; and rituximab plus mycophenolate mofetil.
Studies included	Base case included 17 studies; scenario analysis include 2 further studies.
Outcomes	Complete renal response; partial renal response.

Results	Results suggest that voclosporin plus mycophenolate mofetil is superior to all comparators for complete renal response rate but similar to them for partial renal response rate. These data were applied to the economic analysis.

CrI = credible interval; OR = odds ratio.

*Other data were also assessed but remain commercially confidential.**

3. Summary of Safety Evidence

Voclosporin is a calcineurin inhibitor immunosuppressant, structurally similar to ciclosporin. A regulatory review noted that the safety of voclosporin appears consistent with other calcineurin inhibitors, with predominantly infections, renal impairment and hypertension. Other calcineurin inhibitor adverse effects include neurotoxicity, electrolyte disturbances, impaired glucose tolerance, diabetes mellitus and malignancies. In patients with lupus nephritis, there is particular concern about the increased frequency of renal adverse events with voclosporin compared with placebo. However, this is considered manageable through careful monitoring.[5]

In pooled analyses of data from patients who received the licensed dose of voclosporin (23.7mg twice daily) or placebo in AURORA-1 and AURA-LV median duration of treatment was 357 and 343 days in the respective groups. In the voclosporin and placebo groups, treatment-emergent adverse events were reported by 91% (244/267) and 87% (232/266) of patients, respectively, and were considered treatment-related in 47% and 23%. In the respective groups, 23% and 19% had serious adverse events (treatment-related in 4.5% and 3.4%) and 20% and 14% had severe adverse events. Adverse events lead to a dose modification in 46% and 25% of patients in the respective groups and lead to study treatment discontinuation in 14% and 13% (treatment-related in 7.5% and 2.6%). Adverse events leading to death were reported in 3.0% and 1.5% of patients, respectively, with none considered related to study treatment.[5]

In the pooled analyses, infection and infestations were reported more frequently with voclosporin than placebo, 62% versus 55%, as were adverse events in several systems, including disorders of: gastro-intestinal tract, 45% versus 35%; nervous system, 28% versus 16%; skin and subcutaneous tissue, 25% versus 20%; blood and lymphatic system, 20% versus 16%; vascular system, 21% versus 14%; respiratory tract, 20% versus 9.4%; eye, 9.4% versus 4.9%; and cardiac, 7.5% versus 5.3%.[5]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Evidence for the voclosporin-based regimen was available from well-conducted double-blind, placebo-controlled phase II and III studies. As these studies included mycophenolate mofetil as concomitant therapy, there is direct comparative evidence for voclosporin versus the main current standard treatment.[5-7]
- Addition of voclosporin to standard of care (mycophenolate mofetil plus glucocorticoids) improved renal response rates by about 20% at Week 52 in the phase III study with benefits maintained after a further two years' long-term follow-up. The difference was mainly due to a difference in the proportion of patients achieving reduction in proteinuria to a UPCR ≤0.5mg/mg. Reductions in proteinuria are associated with improved long-term renal outcomes and the benefits of voclosporin were considered clinically relevant by a regulatory authority. Renal responses were maintained up to three years in an extension study.[5-7]
- Voclosporin is the first calcineurin inhibitor licensed specifically for lupus nephritis.[3]
- Voclosporin is second medicine (after belimumab) to be licensed for the treatment of lupus nephritis in combination with another immunosuppressant. In April 2022, SMC issued advice (SMC2483) that in the absence of a submission from the holder of the marketing authorisation: belimumab (Benlysta®) is not recommended for use within NHSScotland. The use of two concomitant immunosuppressants may represent a change in practice.

4.2. Key uncertainties

- Apart from reduction in proteinuria, there were generally no substantial differences between voclosporin and placebo for components of the composite primary, which included: rescue medication, estimated glomerular filtration rate (eGFR) change and prednisolone dose.[5-7]
- Over the long-term, in patients who continued treatment into the AURORA-2 study, there appeared to be no difference in rates of renal flares or severe renal flares.[5] However, the number of patients included in this analysis was modest (n=174) and the study was not designed or powered to assess this outcome.
- In the AURORA-1 study, pre-specified subgroup analysis by mycophenolate mofetil use at screening suggest that the population was heterogeneous. In the subgroup of patients who were not taking mycophenolate mofetil at screening (that is, they commenced it at the start of the study), the Week 52 renal response rate OR was 1.3 (95% CI: 0.6 to 2.5), suggesting limited benefit relative to mycophenolate alone in patients commencing initial treatment for active disease.[6,8] There was no information on duration of mycophenolate mofetil treatment or response to it in patients receiving this at screening.[5] Therefore, it was not possible to define the patient group likely to achieve the best responses, OR 5.8 (95% CI: 2.8 to 11.9), with voclosporin.

- Almost all patients had previous treatment for lupus nephritis at some time prior to the AURORA-1 and AURA-LV studies.[5-7] There is a paucity of data on the use of voclosporin for active lupus nephritis in treatment-naïve patients.
- The NMA was limited by considerable heterogeneity across the included studies in design, duration, size and inclusion criteria. There was heterogeneity across study populations in class of lupus nephritis, disease activity and prior treatment. Of particular importance, the definitions of outcomes, CRR and PRR, differed across the studies and this creates uncertainty in estimates of treatment effects. Many of the medicines are used 'off-label' to treat active lupus nephritis and the doses varied across the studies, as did the concomitant corticosteroid regimens, which adds to heterogeneity. A potential comparator, ciclosporin, was not included in the NMA. Due to these limitations, the company's conclusions are uncertain.

4.3. Clinical expert input

Clinical experts consulted by SMC consider that voclosporin is a therapeutic advance in the treatment of lupus nephritis due to the improved outcomes relative to current standard of care. They expect that it would be used in practice for the first-line treatment of lupus nephritis and note that the doses of corticosteroids used with the voclosporin and mycophenolate mofetil regimen may be lower than those in the current standard of care.

4.4. Service implications

Clinical experts consulted by SMC note that voclosporin is not likely to be associated with service implications as it is administered orally.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Lupus UK and the National Kidney Federation, which are both registered charities.

- Lupus UK has received 0.97% pharmaceutical company funding in the past two years, including from the submitting company. The National Kidney Federation has received 9% pharmaceutical company funding in the past two years, with none from the submitting company.

- Lupus nephritis (and associated symptoms of SLE) often has a significant impact on the lives of people with the disease and their close family. It also represents a risk of early mortality. As a condition that can affect any major organ in the body, patients face a number of different impacts on their day to day life, including their employment and relationships with family and friends.

- Treatments can be used to slow the course of lupus nephritis but are not always effective and may not be tolerated well by all. The negative impact of long and short term side effects from glucocorticoids can be a particular problem for patients.

- Voclosporin offers an additional treatment option, representing hope for those with active disease who do not respond to standard therapy. Voclosporin is an orally-administered therapy, which is convenient for patients.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (67 years)
Population	The analysis addresses an adult patient population with active class III, IV lupus nephritis. 87.7% of patients entered in the model are female, and the mean age is 33 years.
Comparators	The submitting company highlighted a 'main' comparison between mycophenolate mofetil (MMF) alone and voclosporin + MMF (V+MMF), however, additional comparators recommended in EULAR guidelines (cyclophosphomide, rituximab +MMF, tacrolimus), were included via network meta-analysis indirect comparison. The focus on MMF is noted as due to issues relating to severity and toxicity of other comparators, or place in treatment pathway.
Model description	The analysis is based on a Markov model with states of CKD1-3a, CKD3b-4, and CKD5 (end stage renal disease), and death. Within CKF1-3a there are substates of active disease (AD), and partial (PR) and complete response (CR). Patients transition between these substates based on AURORA data (transition probabilities are extracted based on the non-parametric count method); these substates are not addressed in the base case for CKD3b-4. Transitions to more advanced states are based on clinical opinion in the absence of AURORA data over these stages.Treatment discontinuation based on parametric analysis of AURORA data is applied for V+MMF and MMF, though other comparators were assumed not to be subject to discontinuation.
Clinical data	The majority of clinical data were taken from the pivotal AURORA 1 and AURORA 2 studies. The observed transitions up to 36 months between AD, PR, and CR for MMR in CKD1-3a are adjusted by NMA odds ratio for PR and CR for indirect comparators.
Extrapolation	Extrapolation beyond this point employs the average of month 30 and 36 data points. For V+MMF a 1:1 weighting of the two AURORA arms is applied (varied in scenario analysis) to "wane" the initial treatment effect.
Quality of life	Quality of life data in AURORA was collected through LN PRO and SF-36. The latter was mapped to EQ-5D-3L using Rowen et al's (2009) system. Mixed models were fitted to the mapped data generating state specific utility estimates without attribution of any direct treatment related utility differences. Baseline utilities were adjusted to decline throughout the model with age.
Costs and resource use	Induction and subsequent maintenance therapy medicine costs were included, with assumptions as to the latter regarding the pattern of treatment dependent on induction therapy. For indirect comparators patients were assumed to continue on therapy to a maximum timepoint of 36 months, with subsequent maintenance

	therapy conditional on type of prior therapy. This was also the maximum applied for V+MMF, however, actual treatment duration is shorter due to discontinuation applied for V+MMF. Costs associated with adverse events were sourced from NHS schedule of costs. Resource use frequencies were assumed to vary by disease stage.
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case results are presented in Table 6.2.

Table 6.2: Base-case results with PAS

V + MMF vs comparator:	Pairwise incremental cost-effectiveness ratio (ICER) £/QALY
MMF	£19,794
L-CYC	£3,717
H-CYC	£2,870
AZA	£16,264
RTX + MMF	£7,480
TAC + MMF	£15,205
TAC	£14,238

Abbreviations: AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; L-CYC = low-dose CYC; H-CYC = high-dose CYC; MMF = mycophenolate mofetil; PAS= patient access scheme; QALYs = quality-adjusted life years; RTX = rituximab; TAC = tacrolimus; VCS = voclosporin

6.3. Sensitivity analyses

Key scenarios are summarised in Table 6.3. The company presented the ten most influential sensitivity analyses for parameter uncertainty for V+MMF vs MMF; these included age, transition from CKD1-3a to 3b-4, and the probability of death in CKD1-3a. ICERs ranged between £16,323 and £26,657.

Table 6.3: Scenario analyses with PAS

Scenario		ICER (£/QALY)
#	Base case	£19,794
1 b)	Time horizon: 40 years	£21,249
3	Treatment duration and efficacy: 18 months	£5,422
4 a)	Utilities: CKD 1-3a based on literature	£18,775
5 a)	TTD: exponential	£20,570
7 a)	Waning for voclosporin CR: 100% MMF	£24,754
7 c)	Waning for voclosporin CR: 80% MMF, 20% voclosporin + MMF	£22,582
7 j)	Waning for voclosporin CR: 100% voclosporin + MMF	£16,086

6.4. Key strengths

The analysis is based on clinical data that shows a notably better response for voclosporin plus mycophenolate mofetil than mycophenolate mofetil alone.

6.5. Key uncertainties

There are a number of limitations associated with the analysis.

- The clinical data from AURORA 1 and 2 is represented though non-parametric count-based methods applied for individual model cycles; due to patient/event numbers this may lead to uncertainty that the submitting company was unable to overcome in its attempts to employ alternative methods. There is uncertainty relating to the pre-screening use of mycophenolate mofetil as noted above.
- Longer-term extrapolation relies on arbitrary assumptions relating to application of year-3 data from AURORA 2. This risks conflation of short-term outcomes following induction therapy with long-term maintenance therapies. However, additional scenario analyses provided some evidence that the effect of less optimistic assumptions may be limited.
- There is uncertainty over anticipated treatment durations, which the submitting company acknowledges.
- The model structure does not address the potential for longer-term treatment involving attempted re-induction of response, adding to the uncertainty over long-term model outcomes.
- There is some uncertainty as to whether the Kaplan-Meier for discontinuation fully aligns with response. Discontinuation was not applied for secondary comparators.

*Other data were also assessed but remain commercially confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted voclosporin for use in NHSScotland.

8. Guidelines and Protocols

In 2018, the British Society for Rheumatology (BSR) published the BSR guideline for the management of SLE in adults.[3]

9. Additional Information

9.1. Product availability date

30 November 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Voclosporin Mycophenolate	23.7mg orally twice daily 1g orally twice daily	14,530

Costs from BNF online on 22 June 23. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1,217 patients eligible for treatment with voclosporin in year 1, rising to 1,454 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

1. Otsuka Pharmaceutical (UK) Ltd. Voclosporin soft capsules (Lupkynis®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 18 December 2022

2. Roche Products Ltd. Mycophenolate mofetil capsules (CellCept®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 28 July 2022

3. Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018; 57(1): e1-e45

4. Markowitz GS, D'Agati VD. Classification of lupus nephritis. Current Opinion in Nephrology and Hypertension 2009; 18: 220–25

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6. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2021; 397: 2070-80

7. Rovin BH, Solomons N, Pendergraft WF, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019; 95(1): 219-31.

8. Otsuka. Clinical study report for AURORA-1, tables and figures, data-on-file.

This assessment is based on data submitted by the applicant company up to and including 19 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a

patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.