5.02 AVACOPAN, Capsule 10 mg, Tavneos®, VIFOR PHARMA PTY LIMITED.

1 Purpose of Submission

1.1 The Category 1 submission requested General Schedule Authority Required listing for avacopan for the treatment of severe active granulomatosis with polyangiitis (GPA) and severe active microscopic polyangiitis (MPA) in combination with rituximab or cyclophosphamide/azathioprine.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus glucocorticoids (GC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with newly diagnosed or relapsed ANCA-associated vasculitis severe active granulomatosis with polyangiitis (GPA) and severe active microscopic polyangiitis (MPA) defined as at least one major or three non-major items or at least two renal items of haematuria and proteinuria on the Birmingham Vasculitis Activity Score (BVAS)
Intervention	Avacopan in combination with rituximab (both induction and maintenance) or cyclophosphamide (induction) /azathioprine (maintenance)
Comparator	Glucocorticoids (GC) which is used as standard of care (SOC) concomitantly with rituximab or cyclophosphamide /azathioprine
Outcomes	Primary • Induce and sustain remission Secondary • Glucocorticoid-induced toxicity • Evaluate rapidity of response in the avacopan group compared to the prednisone group • Evaluate the safety in the avacopan group compared to the prednisone group • Health-related quality of life changes • Assess changes in parameters of renal disease • Assess changes in cumulative organ damage
Clinical claim	Avacopan is superior to standard of care for efficacy Avacopan is superior to standard of care for safety

Source: Table 1-1, p26 of the submission.
Abbreviations: ANCA, antineutrophil cytoplasmic autoantibody; BVAS, Birmingham Vasculitis Activity Score; GC, glucocorticoids, GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; SOC, standard of care.

2 Background

Registration status

2.1 Avacopan was TGA registered on 17 January 2023 for use in combination with a rituximab or cyclophosphamide-based regimen, for the treatment of adults with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

2.2 Avacopan was approved by the Food and Drug Administration (FDA) of the United States in October 2021 and was authorised for use in the European Union by the European Medicines Agency (EMA) in November 2021. Avacopan was assessed by the United Kingdom National Institute for Health and Care Excellence (NICE) in September 2022. The NICE recommendation was: "Avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults[1]".

For more detail on PBAC's view, see section 7 PBAC Outcome.

3 Requested Listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AVACOPAN					
Avacopan 10mg, capsules	$10,727.28 published price $[redacted] effective price	1	180	5	Tavneos, CSL Vifor

Source: Table 1-6, p40 of the submission.
Abbreviations: Max, maximum; qty, quantity, rpts, repeats.

Category / Program: Section 85
Prescriber type: ☒Medical Practitioners
Restriction type: Authority Required (STREAMLINED)
Severity: Severe active
Condition: Granulomatosis with polyangiitis or microscopic polyangiitis
Indication: Severe active granulomatosis with polyangiitis or severe active microscopic polyangiitis
Treatment Phase: Induction or reinduction of remission
Clinical criteria:
The treatment must be for the induction or reinduction of remission
AND
The treatment must be in combination with a cyclophosphamide or rituximab regimen,
AND
Patient must have severe, active disease defined as at least one major or three non-major items or at least two renal items of haematuria and proteinuria on the Birmingham Vasculitis Activity Score (BVAS),
Diagnosis should be made according to the Chapel Hill Consensus Conference Nomenclature of the Vasculitides with anti-neutrophil cytoplasmic antibody (ANCA) positive serology.

[1] "Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis – technology appraisal guidance". Sep 2022. National Institute for Health and Care Excellence. Available at: www.nice.org.uk/guidance/ta825

Category / Program: Section 85
Prescriber type: ☒Medical Practitioners
Restriction type: Authority Required (STREAMLINED)
Severity: Severe active
Condition: Granulomatosis with polyangiitis or microscopic polyangiitis
Indication: Severe active granulomatosis with polyangiitis or severe active microscopic polyangiitis
Treatment Phase: Maintenance therapy
Clinical criteria:
The treatment must be for maintenance therapy
AND
Patient must have previously received this drug for induction of remission for this condition
AND
Patient must have responded to this drug for this condition defined as BVAS score of 0

Category / Program: Section 85
Prescriber type: ☒Medical Practitioners
Restriction type: Authority Required (STREAMLINED)
Severity: Severe active
Condition: Granulomatosis with polyangiitis or microscopic polyangiitis
Indication: Severe active granulomatosis with polyangiitis or severe active microscopic polyangiitis
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]
AND
The treatment must be for the induction or reinduction of remission
AND
The treatment must be in combination with a cyclophosphamide or rituximab regimen,
AND
At the time of non-PBS subsidised treatment initiation, patient must have had severe, active disease defined as at least one major or three non-major items or at least two renal items of haematuria and proteinuria on the Birmingham Vasculitis Activity Score (BVAS)
Diagnosis should be made according to the Chapel Hill Consensus Conference Nomenclature of the Vasculitides with anti-neutrophil cytoplasmic antibody (ANCA) positive serology.
Treatment criteria: Patient must be undergoing continuing treatment with this drug where non-PBS subsidised treatment was for induction or reinduction of remission

Category / Program: Section 85
Prescriber type: ☒Medical Practitioners
Restriction type: Authority Required (STREAMLINED)
Severity: Severe active
Condition: Granulomatosis with polyangiitis or microscopic polyangiitis
Indication: Severe active granulomatosis with polyangiitis or severe active microscopic polyangiitis
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]
AND
The treatment must be for maintenance therapy
AND
Patient must have previously received this drug for induction of remission for this condition

AND
Patient must have responded to this drug for this condition defined as BVAS score of 0
Treatment criteria: Patient must be undergoing continuing treatment with this drug where non-PBS subsidised treatment was for maintenance therapy

Source: Tables 1-7 to 1-10, pp41-43 of the submission
Abbreviations: BVAS, Birmingham Vasculitis Activity Score; PBS, Pharmaceutical Benefits Scheme

3.1 The submission has proposed a special pricing arrangement (SPA) with an effective price that is % lower than the published price. The effective AEMP and DPMQ prices of avacopan are $ and $, respectively.

3.2 The proposed PBS listing for induction treatment does not specify a limit on the number of times avacopan can be used for reinduction following relapse. Until longer-term safety and efficacy data for avacopan are available for multiple relapsed ANCA-associated vasculitis, the evaluation questioned whether multiple inductions would be appropriate. The Pre-Sub-Committee Response (PSCR) argued that incremental improvements in treatment have meant GPA and MPA have evolved into chronic, relapsing conditions that are treated with reinduction of previously efficacious therapy. The ESC considered that, on balance, avacopan would likely be suitable for re-induction therapy based on the mechanism of action.

3.3 The proposed PBS listing for maintenance treatment does not state that avacopan should be used in combination with other treatments, despite the TGA approved indication stating that avacopan should be used 'in combination with a rituximab or cyclophosphamide-based regimen'. The TGA approved indication does not specify which phase of treatment avacopan should be used for (induction, reinduction or maintenance). The PSCR contends that the PBS restriction requested (induction and maintenance) is aligned to use in the clinical trial and recent EULAR guidelines (Hellmich et al. 2022). The ESC disagreed with the PSCR and advised that that use of avacopan as monotherapy was not consistent with TGA approval, international guidelines (see paragraph 4.4) nor the evidence presented in the submission (see paragraph 6.21).

3.4 The listing proposed referring PBS eligibility to two documents that are not authored by the PBAC nor the Australian Government. These were: (1) the Chapel Hill Consensus Conference (CHCC) Nomenclature of the Vasculitides' and (2) the Birmingham Vasculitis Activity Score (BVAS). The effect of this would be to delegate the determination of PBS eligibility, in part, to an organisation that is not Government. The Secretariat advised that where reference to external documents is proposed, consideration to whether the reference is avoidable should be undertaken before a reference is made. For example, in the proposed maintenance therapy restriction, there was the requirement that the patient must have responded to this drug for this condition defined as BVAS score of zero – consideration should be given to describing in simple language what a BVAS score of zero says about the patient or condition instead of referring to a BVAS score. If it is determined that it is not possible to provide a simple translation as to what the BVAS score says about the patient or condition, then the listing needs to be clear on: (i) the version or edition of the BVAS instrument

being referred to, (ii) the source or location of the BVAS instrument, and (iii) access to the BVAS instrument for prescribers and anybody who is not a prescriber. This also applies to any other instrument, document, index, scoring system or guideline that is proposed in the listing.

For more detail on PBAC's view, see section 7 PBAC Outcome.

4 Population and Disease

4.1 ANCA-associated vasculitis (AAVs) are a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. AAVs are classified based on antibody status or clinical phenotype: status of PR3-ANCA+ is linked to granulomatosis with polyangiitis (GPA) whereas MPO-ANCA+ is linked to microscopic polyangiitis (MPA). AAVs can involve many organs, with the kidneys, respiratory tract, nose/sinuses, eyes, skin, and nervous system most commonly affected. Respiratory and kidney failure can occur in patients with very severe active disease. Other complications of the disease include hearing loss, nasal bridge collapse, and subglottic tracheal stenosis. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset. AAVs can present at any age, with diagnosis commonly occurring between the age of 55 to 74.

4.2 Treatment phases for AAV are induction, which aims to induce disease remission, maintenance, which aims to prevent disease relapse and further organ damage, and reinduction, which aims to reinduce remission following disease relapse. For induction treatment, either cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are considered the standard of care (SOC). For maintenance treatment, tapered glucocorticoids in combination with either rituximab or azathioprine are used. These treatments reduce mortality but are not curative and over one-third of patients will experience a relapse within 18 months of induction of remission[2]. For patients in remission who have a subsequent relapse, treatment consists of reinduction with rituximab or cyclophosphamide (limited by its cumulative lifetime toxicity) in combination with high dose glucocorticoids.

4.3 Avacopan is proposed to be used concomitantly with other immunosuppressive therapy (rituximab, cyclophosphamide or azathioprine), in a similar manner to glucocorticoids.

4.4 The ESC noted that the EULAR 2022 recommendations for the management of ANCA-associated vasculitis (AAVs) stated that:

[2] Grayson, P. C*., et al.* (2013). "New features of disease after diagnosis in 6 forms of systemic vasculitis." J Rheumatol **40**(11): 1905-1912.

- Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.
- For maintenance of remission of GPA and MPA, after induction of remission with either rituximab or cyclophosphamide, we recommend treatment with rituximab. Azathioprine or methotrexate may be considered as alternatives.

The ESC noted that the EULAR 2022 recommendation favouring use of rituximab for maintenance treatment was based on the results of the MAINRITSAN and RITAZAREM trials. Regular 6 monthly dosing of rituximab was used in the MAINRITSAN trial with the ESC noting that the guidelines also referred to tailored dosing of rituximab based on biomarkers. The ESC considered that there was no indication in the EULAR 2022 guidelines that avacopan should be used as monotherapy in a maintenance setting. In addition, the ESC noted that the EULAR 2022 guidelines provide evidence for reduced-dose prednisolone regimens as part of regimens for induction of remission.

4.5 Avacopan is a selective antagonist of the human complement 5a receptor (C5aR1 or CD88) and competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a. The specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation and migration, and decreases adherence to sites of small blood vessel inflammation, and vascular endothelial cell retraction and increased permeability.

For more detail on PBAC's view, see section 7 PBAC Outcome.

5 Comparator

5.1 The submission nominated glucocorticoids as the comparator. The submission suggested that to induce remission, avacopan should be administered with concomitant therapy (either rituximab or cyclophosphamide) at the choice of the treating physician to reduce or replace glucocorticoids. To sustain remission, avacopan could be used as a monotherapy or used concomitantly with maintenance regimen (typically azathioprine, rituximab or glucocorticoids at reduced doses).

5.2 The ESC agreed with the evaluation that the nominated comparator glucocorticoids was considered appropriate in the induction phase.

5.3 The appropriateness of glucocorticoids as the nominated comparator in the maintenance phase will depend on whether avacopan is used in combination or as monotherapy. The TGA approved Product Information and PICO statement only describe avacopan used as combination therapy, whereas the proposed clinical algorithm and PBS restriction permits monotherapy in maintenance phase. If avacopan monotherapy is deemed appropriate for maintenance treatment, then other comparators will be relevant (such as tapered glucocorticoids plus azathioprine, tapered glucocorticoids plus methotrexate, and tapered glucocorticoids plus rituximab). The ESC advised that a comparison with 'no treatment' in the maintenance

setting was not consistent with clinical practice nor international guidelines (EULAR 2022), and hence was not appropriate.

For more detail on PBAC's view, see section 7 PBAC Outcome.

6 Consideration of the Evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the relapsing nature of the disease and the impact of a relapse on renal function. The clinician described the significance of a decrement of 10 mL/min in eGFR and the risk of dialysis that can occur with a relapse. The clinician indicated that rituximab maintenance is now commonly used in clinical practice. The clinician outlined how avacopan would likely be used in practice and the preference for clinician discretion in determining duration of therapy and reinduction. The clinician emphasised the importance of reducing the adverse effects associated with glucocorticoid use and the availability of alternative treatment options for patients that do not tolerate currently available therapies. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease. The PBAC confirmed that the trial design which included the rapid weaning of study supply of GC after week 20 did not reflect clinical practice.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The health care professional comments described the benefits of using avacopan combined with rituximab or cyclophosphamide in terms of a reduction in glucocorticoid adverse effects. The health care professional input also recommended avacopan should only be available via a specialist experienced in the treatment of vasculitis such as a nephrologist, immunologist or rheumatologist.

6.3 The PBAC noted the advice received from the Australasian Society of Clinical Immunology and Allergy (ASCIA) regarding the limitations of current treatments used to manage patients with vasculitis disorders including GPA and MPA. ASCIA noted that there are considerable costs to patients and the healthcare system due to delayed or inadequate treatment of severe GPA and MPA.

6.4 The PBAC noted the advice received from the Australian Rheumatology Association (ARA) which stated there is a great demand for additional therapies for AAV patients with inadequately controlled disease. The ARA highlighted that the goal of treatment is the induction and maintenance of long-term remission, as this is not a curable condition. The ARA stated that much of the treatment related morbidity in induction therapy can be attributed to glucocorticoids. The ARA indicated the potential benefits of avacopan after one year of treatment are: superior sustained remission compared with standard of care; improvement in kidney function and delayed time to diagnosis;

and improved quality of life and reduced toxicity compared to standard of care.

6.5 The PBAC noted the advice received from the Australian and New Zealand Vasculitis Society (ANZVASC) that severe glucocorticoid adverse effects are common in the treatment of severe AAV due to the need for high doses of these agents. ANZVASC described the use of lower dose protocols to minimise exposure to high-dose glucocorticoids, but stated that many patients still experience severe steroid adverse effects. The ANZVASC stated the complete wean off prednisolone by week 21 in the ADVOCATE trial was faster than steroid weans in prior trials including PEXIVAS and was not consistent with general clinical practice in Australia where prednisolone is stopped around 12 months in the majority of AAV patients. ANZVASC stated this may have led to more relapses in the control arm by 12 months in the ADVOCATE trial. ANZVASC highlighted that treatment with avacopan in the trial was associated with lower glucocorticoid adverse events and complications. ANZVASC highlighted that patients in the advocate arm received 37%, not 0% of the cumulative amount of glucocorticoids that patients in the prednisolone arm received. As such, ANZVASC stated it is not known how patients with severe disease might fare if they are treated with avacopan alone. In addition, ANZVASC indicated the safety and clinical effects of avacopan beyond 52 weeks were not addressed in the trial and therefore its role in maintenance therapy remains unclear. ANZVASC stated that the ability to treat AAV with avacopan combined with rituximab or cyclophosphamide, thereby allowing avoidance of high, cumulative glucocorticoids would be an advantage to a subgroup of patients with this condition.

6.6 The PBAC noted that the advice from organisations was supportive of the evidence provided in the submission regarding the potential benefits of avacopan in reducing GC use, however, the PBAC remained concerned the comparative evidence for treatment beyond 6 months was not sufficient to support other claims regarding significant benefits in remission and improvements in renal function.

Clinical trials

6.7 The submission was based on one head-to-head trial (ADVOCATE) comparing avacopan + SOC to prednisone + SOC in patients with severe active GPA or MPA (N=331). All patients received one of three SOC regimens including IV or oral cyclophosphamide followed by azathioprine or mycophenolate mofetil from Week 15 onwards or weekly IV rituximab for the first 4 weeks followed by no treatment. Although discouraged, the ADVOCATE trial protocol permitted the use of non-study supplied GCs (i.e., GC use other than the prednisone/prednisone-matching placebo provided under the protocol) in certain clinical situations. The GC used in the clinical trial was prednisone. The ESC noted the ADVOCATE trial compared avacopan + SOC with prednisolone + SOC for induction only as the use of study supplied prednisolone was rapidly weaned over 20 weeks. The ESC considered that in the induction phase, avacopan was being used as part of a strategy to reduce exposure to glucocorticoids. The ESC agreed with the PSCR that the ADVOCATE trial included a maintenance phase

and noted this included a comparison with patients who were on a background of either azathioprine/mycophenolate mofetil (following cyclophosphamide) or no further treatment (following rituximab induction). The ESC considered the latter was not consistent with clinical practice, nor international guidelines (EULAR 2022) and, therefore, had no relevance to the current submission.

6.8 The submission used the study results of the CLEAR and CLASSIC trials as additional evidence to support the clinical claims presented in the ADVOCATE trial. The CLEAR and CLASSIC trials were phase 2 randomised trials with a duration of 12 weeks and study populations N<100. The results of these trials were generally consistent with the pivotal trial and are not reported on further in the ESC advice.

6.9 Details of the ADVOCATE trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ADVOCATE NCT02994927	A Randomized, Double-blind, Active-controlled, Phase 3 study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine.	June 2020
	Cortazar FB, Niles JL, Jayne DRW et al. Renal recovery for patients with antineutrophil cytoplasmic autoantibody-associated vasculitis and low estimated GFR in the ADVOCATE trial of avacopan.	*Kidney Int Rep* 2023 (in press)
	Jayne DRW, Merkel PA, Schall TJ et al. Avacopan for the treatment of ANCA-associated vasculitis.	*NEJM* 2021; 384:599-609
CLEAR (NCT01363388) Excluded as phase 2 trial	CLEAR CSR: Avacopan in combination with CYC or RTX without GCs or avacopan in combination with CYC or RTX with two thirds reduced starting dose of GCs versus placebo in combination with CYC or RTX with full starting dose of GCs in adults with newly diagnosed or relapsing MPA or GPA	*CSR_CL002_168*
CLASSIC (NCT02222155) Excluded as phase 2 trial	CLASSIC CSR: Low-dose avacopan in combination with CYC or RTX (with or without GCs) or high-dose avacopan in combination with CYC or RTX (with or without GCs) versus placebo in combination with CYC or RTX in adults with newly diagnosed or relapsing MPA or GPA	*CSR_CL003_168*

Source: Table 2.3, p47 of the submission.
Abbreviations: ANCA, Anti-Neutrophil Cytoplasmic Antibody; GFR, glomerular filtration rate.

6.10 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)
Avacopan + SOC vs. prednisone + SOC					
ADVOCATE	331	R, DB, DD, AC, MC 52-week treatment period	Low/some concerns	Severe active GPA or MPA	Primary: Disease remission (Week 26) and sustained remission (Week 52) Secondary: GC-induced toxicity (Week 13 and Week 26), rapidity of response (Week 4), HRQoL (Week 13 and Week 26), relapse (Week 52), changes in parameters of renal disease (Week 13, Week 26 and Week 52) and changes in cumulative organ damage (Week 52).

Source: Table 2.7, p55 of the submission, and Attachment 8.

Abbreviations: AC, active-controlled; DB, double-blind; DD, double-dummy; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; HRQoL, health-related quality-of-life; MC, multicentre; MPA, microscopic polyangiitis; R, randomised.

6.11 The submission claimed that there was an overall low risk of bias from the ADVOCATE trial. However, an overall low/some concerns rating for the risk of bias from the ADVOCATE trial is more appropriate given there were some concerns for risk of attrition bias.

6.12 Primary efficacy outcomes of the ADVOCATE trial included disease remission at Week 26 and sustained remission at Week 52. Disease remission at Week 26 was defined as a Birmingham Vasculitis Activity Score (BVAS) score of 0 and not taking GCs for AAV within 4 weeks prior to Week 26. Sustained remission at Week 52 was defined as disease remission at Week 26 and disease remission at Week 52 (i.e., BVAS of 0 and not taking GCs for AAV for 4 weeks prior to Week 52) without disease relapse between Week 26 and Week 52.

6.13 The proposed PBS listing for avacopan differs from the ADVOCATE trial eligibility criteria in two ways: the eGFR threshold and the use of prior therapies. The ADVOCATE trial included patients with an eGFR above 15 mL/minute/1.73 m^2, while the PBS listing does not stipulate a specific threshold. The impact of this difference is minimal as patients with an eGFR below 15 mL/minute/1.73 m^2 (presumed to be experiencing kidney failure and/or on dialysis, in need of dialysis or plasma exchange) are not likely appropriate candidates for avacopan + SOC therapy. This is in accordance with the PI which states that avacopan "has not been evaluated in ANCA-associated vasculitis patients with an estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m^2, who are on dialysis, in need of dialysis, or plasma exchange" (Tavneos PI). The ADVOCATE trial excluded patients based on their high use and timing of other medications or treatment, such as GCs, immunosuppressants, dialysis, and kidney transplant. There are no restrictions on prior medications or treatments in the proposed PBS listing.

6.14 During the 2-week screening period in the ADVOCATE trial, the avacopan + SOC group had a lower percentage of patients with prior GC use (75.3%) compared to the prednisone + SOC group (82.3%). The total prednisone-equivalent dose administered during the 2-week screening period was 907.3 mg for the avacopan + SOC group and 978.0 mg for the prednisone + SOC group. This represents a relatively small clinical difference in GC use and patients with high GC use in the 4 to 6 weeks preceding the trial were excluded. The ESC noted that in the pre-screening period (i.e. during the 12 months prior to the study) that the mean total prednisolone-equivalent was 340.2 mg for the avacopan + SOC group and 485.9 mg for the prednisolone + SOC group. The ESC considered that patients randomized to prednisolone +SOC were likely more dependent on GCs given this difference was already present before they started the trial.

Comparative effectiveness

6.15 The submission used a prespecified 'sequential, gatekeeping procedure' to establish the clinical superiority claims of avacopan + SOC over prednisone + SOC. This was accomplished by meeting pre-defined criteria for non-inferiority and subsequently superiority based on primary outcome results from the ADVOCATE trial.

6.16 The primary efficacy outcomes of the ADVOCATE trial were the proportion of patients with disease remission at Week 26 and the proportion of patients with sustained remission at Week 52. The submission proposed a non-inferiority margin of -0.20 to compare avacopan + SOC with prednisone + SOC; i.e., avacopan + SOC would be considered non-inferior to prednisone + SOC if the difference in the proportion of patients with either remission or sustained remission had a lower bound of the two-sided 95% CI greater than 20 percentage points.

6.17 Secondary efficacy outcomes such as GC-induced toxicity, health-related quality of life, proportion of patients experiencing relapse and time to relapse, and changes in parameters of renal disease were evaluated at different weeks throughout the ADVOCATE trial, with some measured at Week 13, Week 26, and Week 52. The only secondary efficacy outcome with a nominated minimal clinically important difference (MCID) was GC-induced toxicity based on Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS) and Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS) at Week 13 and Week 26. The submission proposed a GTI MCID of 10 points. However, the MCID may be more applicable to GTI-AIS as opposed to GTI-CWS since the data used to calculate the MCID was based on GTI-AIS assessments.

6.18 The primary and secondary efficacy analyses were based on the ITT population (all randomly assigned patients who received at least one dose of blinded study drug/placebo).

6.19 Table 4 presents the results of the primary efficacy outcomes, disease remission and sustained remission, from the ADVOCATE trial. The ESC considered that the week 26 and week 52 results were relevant to induction therapy and maintenance therapy respectively.

Table 4: Results of primary outcomes in the ADVOCATE trial (ITT population)

Outcome	Avacopan + SOC n/N	Prednisone + SOC n/N	Event rate/100 patients		Risk difference, % (95% CI)	Estimate of common difference, % (95% CI)[a]	Non-inferior p-value	Superior p-value
			Avacopan + SOC	Prednisone + SOC				
Disease remission (Week 26)	120/166	115/164	72.3	70.1	2.2 (-7.6, 11.9)	3.4 (−6.0, 12.8)	<0.0001	0.2387
Sustained remission (Week 52)	109/166	90/164	65.7	54.9	10.8 (0.3, 21.3)	12.5 (2.6, 22.3)	<0.0001	0.0066

Source: Table 2.21, p77 of the submission, Table 2.22, p78 of the submission, Table 13, p88 of the ADVOCATE CSR and Table 15, p90 of the ADVOCATE CSR, and calculated during the evaluation.
Abbreviations: CI, confidence interval; SOC, standard of care.
[a] Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights.

6.20 At Week 26, avacopan + SOC was non-inferior to prednisone + SOC in achieving disease remission, however superiority was not demonstrated. The PSCR noted that while the remission is achieved at a rate similar to a prednisolone taper regimen at 26 weeks, a reduction in total steroid burden was evident. The ESC agreed with the PSCR that the total study and non-study supplied GC dosage required during the induction period was lower in avacopan + SOC group (1373.7 mg) relative to prednisone + SOC group (3364.0 mg).

6.21 At Week 52, avacopan + SOC demonstrated superiority to prednisone + SOC in achieving sustained remission with a 12.5% estimate of common difference in the proportion of patients achieving remission (95% CI: 2.6% to 22.3%; p=0.0066 for superiority). The ESC noted that neither arm had study allocated prednisolone beyond 20 weeks. In addition, the ESC noted the sustained remission outcome included patients who were on a background of either azathioprine or mycophenolate mofetil for maintenance (following cyclophosphamide) or no further treatment (following rituximab induction). As outlined in paragraph 6.7, the ESC considered the latter is not consistent with clinical practice, nor international guidelines (EULAR 2022).

6.22 The use of non-study supplied GCs is a potential confounder of remission and sustained remission outcomes. The avacopan + SOC group received a higher average cumulative dose of non-study supplied GCs (1675.5 mg) compared to the prednisone + SOC group (1457.6 mg) during the 52-week treatment period. The overall greater use of non-study supplied GCs was driven by differences observed during the first 26 weeks of treatment, where the avacopan + SOC group had a mean cumulative dose of 1373.7 mg compared to 974.8 mg in the prednisone + SOC group. The PSCR stated that with the presence of active disease during the first 26 weeks, it was not surprising that the use of rescue GC is higher in the avacopan arm as the comparator is GC-based. The PSCR argued that overall, avacopan presents a corticosteroid-sparing treatment option, which will reduce long-term GC use.

6.23 In the ADVOCATE trial analysis, a sensitivity analysis was performed to exclude patients who had high non-study supplied GCs (defined as more than 560 mg prednisone equivalent from Week 26 through Week 52) from the sustained remission analysis. The results of the sensitivity analysis are summarised in Table 5.

Table 5: Pre-specified sensitivity analysis of the proportion of subjects with sustained disease remission excluding subjects with high non-study supplied GC use in the ADVOCATE trial (ITT population)

Outcome	Avacopan + SOC n/N (%)	Prednisone + SOC n/N (%)	Risk difference, % (95% CI)	Estimate of common difference, % (95% CI)[a]	Non-inferior p-value	Superior p-value
Sustained remission (Week 52)	104/138 (75.4)	86/119 (72.3)	3.1 (-7.7, 13.9)	5.0 (-5.6, 15.5)	<0.0001	0.1772

Source: Table 14.2.2.4, p336 of Attachment 9, and calculated during the evaluation.
Abbreviations: CI, confidence interval; SOC, standard of care.
[a] Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights.

6.24 The pre-specified sensitivity analysis showed that avacopan + SOC was non-inferior but not superior to prednisone + SOC at 52 weeks, with an estimated common difference of 5.0 percentage points (95% CI: -5.6 to 15.5; p<0.0001 for non-inferiority, p=0.1772 for superiority). This suggested that the use of non-study supplied GCs was important for the clinical effect of avacopan + SOC and that interpretation of the results was confounded by the permitted use of non-study supplied GCs in all treatment groups. The ESC agreed with the evaluation that the treatment effect observed in the ADVOCATE trial for avacopan + SOC should be interpreted with consideration of this combination use of GCs. The ESC considered the value of the drug would be the more favourable safety profile for avacopan given fewer steroid related adverse events from the overall lower corticosteroid dose.

Subgroup analysis

6.25 Table 6 presents the results of several pre-specified subgroup analyses of the primary efficacy outcome of sustained remission at Week 52 from the ADVOCATE trial.

Table 6: Results of pre-specified subgroup analysis for sustained remission (week 52) in ADVOCATE trial (ITT population)

Outcome	Patient subgroup	Avacopan + SOC n/N (%)	Prednisone + SOC n/N (%)	Estimate of common difference, % (95% CI)
Sustained remission (Week 52)	All patients	109/166 (65.7)	90/164 (54.9)	12.5 (2.6, 22.3)
	SOC treatment			
	Rituximab	76/107 (71.0)	60/107 (56.1)	15.0 (2.2, 27.7)
	Cyclophosphamide	33/59 (55.9)	30/57 (52.6)	3.3 (-14.8, 21.4)
	ANCA type			
	Anti-PR3+	43/72 (59.7)	40/70 (57.1)	2.6 (-13.6, 18.8)
	Anti-MPO+	66/94 (70.2)	50/94 (53.2)	17.0 (3.3, 30.7)
	Disease status			
	Newly diagnosed	70/115 (60.9)	66/114 (57.9)	3.0 (-9.7, 15.7)
	Relapsed	39/51 (76.5)	24/50 (48.0)	28.5 (10.4, 46.6)
	AAV type			
	GPA	56/91 (61.5)	52/90 (57.8)	3.8 (-10.5, 18.0)
	MPA	53/75 (70.7)	38/74 (51.4)	19.3 (4.0, 34.7)
	Renal disease at baseline			
	With renal disease	91/134 (67.9)	76/134 (56.7)*	11.2 (-0.3, 22.7)
	Without renal disease	18/32 (56.3)	14/30 (46.7)*	9.6 (-15.2, 34.4)

Source: Table 2.21, p77 of the submission, Table 2.33, p97 of the submission, Table 14.2.2.9, pp340-341 of Attachment 9, and corrected during the evaluation (*).

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic autoantibody; CI, confidence interval; GPA, granulomatosis with polyangiitis; ITT, intent to treat; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; SOC, standard of care.

6.26 The pre-specified subgroup analyses suggest that avacopan + SOC may not be as effective in achieving sustained remission at Week 52 compared to prednisone + SOC for certain subgroups including those who were receiving cyclophosphamide as part of their SOC regimen, those who tested positive for anti-PR3, newly diagnosed patients, and patients with GPA. Although these patients would be eligible for PBS listing, these subgroups show weaker treatment effect in achieving sustained remission from avacopan + SOC over the comparator. Furthermore, the proportion of patients with MPA in Australia is lower than in the ADVOCATE trial, which may lead to smaller treatment impact in the Australian setting. It is unclear what proportion of patients in Australia will receive rituximab or cyclophosphamide SOC in combination with avacopan, as well as the distribution of patients based on newly diagnosed versus relapsed, and anti-PR3+ versus anti-MPO+. The PSCR noted that although these subgroups were pre-defined in ADVOCATE, the trial was not randomised, powered, or statistically gated to demonstrate differences across subgroups and argued that given the overlap across all subgroups no conclusions can be drawn from these data. The ESC considered the results for SOC treatment indicated that for those receiving either azathioprine or mycophenolate mofetil for maintenance therapy (i.e. cyclophosphamide SOC) there may be no benefit in sustained remission at 52 weeks with the addition of avacopan. The ESC considered the results for SOC indicated it was

likely that the modest 12.5% difference in the proportion of patients achieving sustained remission between the two treatment arms (see paragraph 6.21) was likely driven by those who were not on any maintenance therapy after rituximab.

Secondary outcomes

6.27 Table 7 presents the results of the secondary efficacy outcomes of GC-induced toxicity, health-related quality of life (HRQoL) based on EuroQuality of Life Domains-5 Levels (EQ-5D-5L), relapse and changes in parameters of renal disease in patients with renal disease from the ADVOCATE trial. The extent of missing data was potentially important for several secondary outcomes in the ADVOCATE trial, including GC-induced toxicity, HRQoL, and changes in parameters of renal disease, with rates ranging from 6.7% to 20.9% depending on the treatment group and outcome measure.

Table 7: Results of secondary outcomes in the ADVOCATE trial (ITT population)

Outcome	Avacopan + SOC (N=166)	Prednisone + SOC (N=164)	Treatment difference % (95% CI)	P-value
GC-induced toxicity				
GTI-CWS (Week 13), LSM ± SE	**25.7 ± 3.4 (n=160)**	**36.6 ± 3.4 (n=161)**	**-11.0 (−19.7, −2.2)**	**0.0140**
GTI-CWS (Week 26), LSM ± SE	**39.7 ± 3.4 (n=154)**	**56.6 ± 3.4 (n=153)**	**−16.8 (−25.6, −8.0)**	**0.0002**
GTI-AIS (Week 13), LSM ± SE	**9.9 ± 3.4 (n=160)**	**23.2 ± 3.5 (n=161)**	**−13.3 (−22.2, −4.4)**	**0.003**
GTI-AIS (Week 26), LSM ± SE	**11.2 ± 3.5 (n=154)**	**23.4 ± 3.5 (n=153)**	**-12.1 (−21.1, −3.2)**	**0.008**
HRQoL				
Score on EQ-5D-5L VAS, change from baseline (Week 26), LSM ± SE	9.1 ± 1.4 (n=153)	5.5 ± 1.4 (n=150)	3.6 (−0.1, 7.2)	0.05
Score on EQ-5D-5L VAS, change from baseline (Week 52), LSM ± SE	**13.0 ± 1.4 (n=149)**	**7.1 ± 1.4 (n=146)**	**5.9 (2.3, 9.6)**	**0.002**
Score on EQ-5D-5L Index, change from baseline (Week 26), LSM ± SE	0.02 ± 0.014 (n=152)	0.00 ± 0.015 (n=146)	0.02 (–0.01, 0.06)	0.22
Score on EQ-5D-5L Index, change from baseline (Week 52), LSM ± SE	**0.05 ± 0.015 (n=149)**	**0.00 ± 0.015 (n=145)**	**0.05 (0.01 to 0.09)**	**0.009**
Relapse				
Relapse after achieving disease remission at Week 26 (Week 52), n/N (%)	9/120 (7.5)	14/115 (12.2)	-4.7 (-14.4, 2.4)	0.0810
Changes in parameters of renal disease in patients with renal disease[a]				
eGFR, ml/min/1.73 m², change from baseline (Week 26), LSM ± SE	**5.8 ± 1.0 (n=121)**	**2.9 ± 1.0 (n=127)**	**2.9 (0.1, 5.8)**	**0.046**
eGFR, ml/min/1.73 m², change from baseline (Week 52), LSM ± SE	**7.3 ± 1.0 (n=119)**	**4.1 ± 1.0 (n=125)**	**3.2 (0.3, 6.1)**	**0.029**
UACR, change from baseline (Week 52), LSM ± SE	0.26 ± 1.1 (n=109)	0.23 ± 1.1 (n=114)	1.12 (0.86, 1.45)	0.3991
Urinary MCP-1 to creatinine ratio, change from baseline (Week 13), LSM ± SE	**0.41 ± 1.06 (n=113)**	**0.48 ± 1.06 (n=120)**	**0.85 (0.72, 0.99)**	**0.0339**
Urinary MCP-1 to creatinine ratio, change from baseline (Week 52), LSM ± SE	0.27 ± 1.06 (n=106)	0.29 ± 1.06 (n=108)	0.90 (0.77, 1.06)	0.2223

Source: Section 2.5, pp78-91 of the submission.

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQuality of Life-5 Domains-5 Levels; GC, glucocorticoids; GTI-AIS,Glucocorticoid Toxicity Index Aggregate Improvement Score; GTI-CWS, Glucocorticoid Toxicity Index Cumulative Worsening Score; HRQoL, health related quality of life; ITT, intent to treat; LSM, least-squares mean; MCP-1, monocyte chemoattractant protein-1; SE, standard error; SF-36v2, Short Form-36 version 2; SOC, standard of care; UACR, urinary albumin:creatinine ratio; VAS, Visual Analogue Scale; VDI, Vasculitis Damage Index.

[a] Patients with renal disease at baseline (based on BVAS). Avacopan + SOC: N=134; prednisone + SOC: N=134.

Bold indicates statistically significant results.

6.28 Avacopan + SOC showed statistically significant improvement in several patient-relevant secondary outcomes, including reduced GC-induced toxicity on both the GTI-CWS and GTI-AIS, improved HRQoL on the EQ-5D-5L visual analogue scale (VAS) and Index score, and improved renal disease parameters.

6.29 There was a clinically significant improvement in GTI-CWS and GTI-AIS at Week 13 and Week 26 since all GTI score improvements were greater than the pre-defined MCID of 10 points. However, the MCID may not be applicable to GTI-CWS since the data used to calculate the MCID was based on GTI-AIS assessments, which could be important considering the differences in their definitions; GTI-CWS measures cumulative GC toxicity, regardless of whether it is permanent or transient, whereas GTI-AIS measures both deterioration and improvement in GC toxicity. The ESC noted that the total study and non-study supplied GC dosage required during the induction period was lower in avacopan + SOC group relative to prednisone + SOC group (see paragraph 6.20) and considered this likely corresponded to improvements in GTI-CWS and GTI-AIS.

6.30 The submission stated that the improvements seen in eGFR rates in patients with renal disease treated with avacopan + SOC may translate into improved renal outcomes when compared to prednisone + SOC. However, while there was an improvement in eGFR rates, other parameters of renal disease such as UCAR at Week 52 and urinary MCP-1 to creatinine ratio at Week 52 did not show any statistical significance in patients with renal disease. The PSCR provided a summary of change in eGFR from baseline to week 52 (Table 8) and argued that across all subgroups avacopan consistently resulted in greater improvement or slower decline compared with prednisolone. The ESC considered the improvement in eGFR were only seen in the subgroup with eGFR <30 (and >15 based on study criteria), occurring during the maintenance phase of the study and became non-significant at week 60 (mean difference 4.2, p =0.1065, Table 14.2.7.1.2 of Attachment 9 ADVOCATE TFLs). The ESC considered it was not clear how much of the benefit in this subgroup was attributable to the group which compared avacopan to no maintenance therapy (i.e. induction with rituximab) and therefore it is unclear if these benefits would be seen in this subgroup of a PBS population.

Table 8 eGFR recovery by eGFR subgroup at baseline

	Week 26				Week 52			
Baseline eGFR (ml/min /1.73m²)	**avacopan**	**prednisone**	**Mean difference**	**P value**	**Avacopan**	**Prednisone**	**Mean difference**	**P value**
Overall	5.8	2.9	2.9	0.046	7.3	4.1	3.2	0.029
<30	10.5	6.4	4.1	0.0361	13.7	8.2	5.6	0.0050
31-59	7.3	5.4	1.9	0.3535	10.5	7.8	2.7	0.2115
>59	-2.6	-6.0	3.4	0.3640	-5.9	-7.5	1.6	0.6721

Source: Table 2, p5 avacopan PSCR

Comparative harms

6.31 Table 9 presents the safety outcomes in the ADVOCATE trial.

Table 9: Summary of key adverse events in ADVOCATE trial (safety population)

Safety outcome	Avacopan + SOC n with event (%) [a] N = 166	Prednisone + SOC n with event (%) [a] N=164	Risk difference, % (95% CI)
Any TEAE	164 (98.8)	161 (98.2)	NR
Maximum severity of TEAE			
Mild	33 (19.9)	34 (20.7)	NR
Moderate	82 (49.4)	68 (41.5)	NR
Severe	39 (23.5)	41 (25.0)	NR
Life-threatening	8 (4.8)	14 (8.5)	NR
Death	2 (1.2)	4 (2.4)	NR
TEAE leading to study medication discontinuation	27 (16.3)	28 (17.1)	NR
SAE	70 (42.2)	74 (45.1)	NR
Acute kidney injury	3 (1.8)	1 (0.6)	NR
Angina pectoris	2 (1.2)	0 (0.0)	NR
Cardiac failure	2 (1.2)	0 (0.0)	NR
Device-related infections	2 (1.2)	0 (0.0)	NR
GPA	5 (3.0)	1 (0.6)	NR
Hyperglycaemia	2 (1.2)	1 (0.6)	NR
Influenza	2 (1.2)	1 (0.6)	NR
Pneumonia	8 (4.8)	6 (3.7)	NR
UTI	3 (1.8)	2 (1.2)	NR
Any treatment-emergent infections	113 (68.1)	124 (75.6)	NR
Any serious treatment-emergent infections	22 (13.3)	25 (15.2)	NR
Any serious treatment-emergent possibly related to study medication (prednisone/placebo)	11 (6.6)	24 (14.6)	NR
Infections and infestations [b]	3 (1.8)	11 (6.7)	NR
Any severe treatment-emergent infection	12 (7.2)	10 (6.1)	NR
Any treatment-emergent infection leading to study withdrawal	4 (2.4)	5 (3.0)	NR
Any treatment-emergent life-threatening infection	1 (0.6)	2 (1.2)	NR
Any treatment-emergent infection leading to death	1 (0.6)	2 (1.2)	NR
Any potentially GC-related AE	**110 (66.3)**	**132 (80.5)**	**-14.2 (-23.7, -3.8)**
Dermatological	**14 (8.4)**	**28 (17.1)**	**-8.6 (-16.2, -1.0)**
Endocrine/metabolic	**23 (13.9)**	**48 (29.3)**	**-15.4 (-24.3, -6.0)**

Source: Table 2.29, p92 of the submission, Table 2.31, p95 of the submission, Table 2.32, p96 of the submission, Table 14.3.1.3.2, pp1924-1930 and Table 14.3.1.6.2, p1990 of Attachment 9.

Abbreviations: AE, adverse event; GC, glucocorticoid; NR, not reported; SAE, serious adverse event; SOC, standard of care; TEAE, treatment-emergent adverse event.

[a] The proportions presented is equivalent to the event rate/100 patients.

[b] Selected safety outcome used in the economic analysis to reflect reduction in mortality due to infection from GC

Bold indicates statistically significant results.

6.32 In the ADVOCATE trial, almost all patients in both the avacopan + SOC and prednisone + SOC groups experienced a treatment-emergent adverse event (TEAE), with a similar proportion of patients in each group (98.8% and 98.2%, respectively). The avacopan + SOC group had a higher incidence of moderate TEAE (49.4%) compared to the prednisone + SOC group (41.5%). There were fewer treatment-emergent infections,

and potentially glucocorticoid-related adverse events (AE) in the avacopan + SOC group compared to the prednisone + SOC group. However, patients in the avacopan + SOC group experienced higher incidences of several SAE including acute kidney injury, angina pectoris, cardiac failure, device-related infections, GPA, hyperglycaemia, influenza, pneumonia, and UTI. There were two (1.2%) deaths in the avacopan + SOC group from worsening of vasculitis and pneumonia and four (2.4%) in the prednisone + SOC group from generalised fungal infection, infectious pleural effusion, acute myocardial infarction, and death of unknown cause.

6.33 There was a statistically significant reduction in potentially GC-related AE in favour of avacopan + SOC compared to prednisone + SOC (treatment difference of -14.2 percentage points; 95% CI -23.7 to -3.8; $p<0.05$). Moreover, a significant difference in the incidence of potentially GC-related adverse events was observed between the avacopan + SOC and prednisone + SOC groups in the endocrine/metabolic (13.9% vs 29.3% respectively) and dermatological (8.4% vs 17.1% respectively) systems.

6.34 The ADVOCATE trial only provided safety evidence supporting the use of avacopan + SOC for treatment induction. Given the relatively short duration of the treatment period (52 weeks), there is no safety evidence on the cumulative risk of reinduction or long-term safety data for maintenance treatment. There was no open-label extension study for the ADVOCATE trial.

Benefits/harms

6.35 On the basis of direct evidence presented by the submission, for every 100 patients treated with avacopan + SOC in comparison with prednisone + SOC over the following treatment periods:

- There would be no difference in disease remission at 26 weeks.
- Approximately 11 additional patients who achieved remission at 26 weeks would achieve sustained remission at Week 52 (Table 4).
- Approximately 15 fewer patients would experience endocrine or metabolic GC-related adverse events at Week 52 (Table 9).
- Approximately 9 fewer patients would experience dermatological GC-related adverse events at Week 52 (Table 9).

Clinical claim

6.36 The submission described avacopan + SOC as superior in terms of effectiveness compared to prednisone + SOC and superior in terms of safety compared to prednisone + SOC. The evaluation considered the comparative efficacy claim was not supported for induction therapy proposed for PBS listing, which covers up to 6 months therapy, as the ADVOCATE trial demonstrated avacopan + SOC was non-inferior to prednisone + SOC at 26 weeks for disease remission. However, in terms of the superior safety claim the ESC agreed with the PSCR that the total study and non-study supplied GC dosage required during the induction period was lower in avacopan + SOC group

(1373.7 mg) relative to prednisone + SOC group (3364.0 mg). The ESC considered this corresponded to a more favourable safety profile for avacopan given fewer steroid related adverse events.

6.37 The evaluation considered that a claim of superior effectiveness and safety compared to prednisone + SOC was not supported for treatment reinduction and maintenance. The key issues were:

- The ADVOCATE trial provided efficacy and safety evidence supporting the use of avacopan + SOC for treatment induction in patients with GPA or MPA, with no evidence for reinduction or maintenance therapy as requested in the PBS listing. The ESC considered the ADVOCATE trial design created uncertainty regarding the phases of therapy incorporated but agreed with the PSCR that the trial included both induction and maintenance therapy. As outlined in paragraph 6.7, the ESC considered the ADVOCATE trial compared avacopan + SOC with prednisolone + SOC for induction only due to the weaning of prednisolone over this period. In addition, the ESC noted the maintenance phase included a comparison with patients who were on a background of either azathioprine or mycophenolate mofetil (following cyclophosphamide) or no further treatment (following rituximab induction). The ESC considered the latter was not consistent with clinical practice, nor international guidelines (EULAR 2022) and, therefore, had no relevance to the current submission.
- Based on the pre-specified subgroup analyses, avacopan + SOC treatment did not substantially improve sustained remission rates at Week 52 for some PBS eligible patients, including those receiving cyclophosphamide, anti-PR3 positive patients, newly diagnosed patients, and those with GPA. The ESC considered that the modest 12.5% difference in the proportion of patients achieving sustained remission between the two treatment arms (see paragraph 6.21) was likely driven by those who were not on any maintenance therapy after rituximab (see paragraph 6.26). The pre-PBAC response contended that for patients with severe active MPA/GPA, a 12.5% difference in sustained remission is substantial (NNT = 9) and translates to a clinically significant 54% reduction in the rate of relapse, in the context of a substantial reduction (2171.4mg) in steroid exposure.
- Higher cumulative dose of non-study supplied GCs in the avacopan + SOC group during the trial, particularly in the first 26 weeks, could confound part of the treatment effect for avacopan + SOC by masking a delayed or less potent treatment effect of avacopan + SOC. The PSCR stated that with the presence of active disease during the first 26 weeks, it was not surprising that the use of rescue GC is higher in the avacopan arm as the comparator is GC-based. The ESC considered the treatment effect observed in the ADVOCATE trial for avacopan + SOC should be interpreted considering the combination use of GCs.
- Acknowledging the evaluation's concerns that there was no evidence for reinduction, the ESC considered that if considered suitable for induction, on

balance, avacopan would likely be suitable for reinduction therapy based on the mechanism of action.

6.38 The PBAC considered that the claim of superior comparative effectiveness was highly uncertain for induction therapy and was not adequately supported by the data for maintenance therapy.

6.39 The PBAC considered that the claim of superior comparative safety was reasonable.

Economic analysis

6.40 The submission presented a modelled cost-utility analysis based on a randomised trial (ADVOCATE trial) directly comparing avacopan + SOC and prednisolone + SOC. A stepped economic evaluation was not presented. Given that the ADVOCATE trial was based on outcomes for sustained remission at 52 weeks, the evaluation considered a stepped approach demonstrating the impact of the transformation of costs and outcomes to include multiple relapse, re-inductions with avacopan and maintenance treatments over 30 years would have been informative.

6.41 Overall, the ESC considered the model was not reliable for decision making given the concerns raised regarding the clinical claims related to induction therapy in paragraph 6.36 and maintenance therapy in paragraph 6.37. The ESC noted that at Week 26, avacopan + SOC was non-inferior to prednisone + SOC in achieving disease remission, however superiority was not demonstrated. The ESC considered that with prednisolone + SOC an appropriate comparator for induction therapy, a cost-minimisation approach that accounts for differences in the adverse event profiles may be an appropriate way forward. The pre-PBAC response strongly disagreed that a cost-minimisation approach was relevant in assessing the cost effectiveness of avacopan and argued that such an approach would undervalue avacopan.

6.42 Table 10 presents the key components of the economic model.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Avacopan + SOC vs prednisolone + SOC
Time horizon	30 years in the model base case versus 52 weeks in trial
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov cohort model
Treatment duration and re-inductions with avacopan	Patients treated for 6 months (induction) followed by 18 months of maintenance (approximately 24 months) and up to 3 inductions (i.e., 2 re-inductions) with avacopan allowed.
Health states	Nine health states in total: Active Disease, Remission (x3), Relapse (x3), ESRD, Death
Cycle length	4 weeks
Transition probabilities	Active disease to relapse and remission: Proportions of patients in remission at week 26 and 52 from the ADVOCATE trial Relapse rate over time: Assumed to be 1/5 (20% reduction) of transition probability after 2 years Transition to ESRD: Based on renal outcomes (eGFR) from the ADVOCATE trial, the association between eGFR and the probability of ESRD using HR of 0.90 from Gercik et al. (2020) and assumed a decrement of 10 mL/min in eGFR for each subsequent relapse based on advice from clinical experts and data from Slot et al. (2003). Background mortality: Based on Australian life tables adjusted to reflect increased risk due to AAV (Wallace et al. 2016), ESRD (Choi et al. 2014) and risk of infection due to GC use (Little et al. 2014 and data from ADVOCATE trial).
Extrapolation method	Treatment effect for avacopan was assumed to wane linearly to match the prednisolone + SOC arm after 52 weeks of cessation of avacopan treatment. 91% of QALYs (and 77% of costs) for the avacopan + SOC arm occur in the extrapolated period. The corresponding distributions for the prednisolone + SOC arm are 90% and 99% respectively.
Health related quality of life	Health state utility values for the following health states were sourced from the ADVOCATE trial: Active disease = 0.702, Remission = 0.778, Relapse = 0.696. For the ESRD health state, the following utility values were applied: Dialysis = 0.458 (Submission's own calculations based on weighted average for dialysis based on utility values for peritoneal dialysis and haemodialysis from NICE 2020 HTA assessment of patiromer for treating hyperkalaemia and proportion of patients for each dialysis type from ANZDATA Annual Report 2021), Transplant = 0.712 (NICE 2020 HTA assessment of patiromer for treating hyperkalaemia), Conservative management = 0.696 (assumed to be the same as utility for relapse health state). Decrement due to GC-related infection = 0.1 (Assumption).

Source: Table 3-1, p102 of the submission.

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody associated vasculitis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GC, glucocorticoid; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; HR, hazard ratio; SOC, standard of care

6.43 Newly diagnosed patients or relapsing patients enter the model in the Active disease health state, where they receive a first course of induction therapy. Depending on response to treatment, patients either move to Remission or Relapse health states. Patients in the Relapse health state can receive a subsequent induction (up to 3 times) and can either remain in Relapse (considered to have refractory disease) or move into

the Remission health state. Patients can develop ESRD at any stage of the disease and stay in the ESRD health state until death or end of the time horizon. Patients can transition into the Death health state from any health state, depending on the background mortality applied.

6.44 The model assumed that all patients with active disease who did not respond to the first induction would transition into the Relapse 1 health state for an opportunity to be re-induced with avacopan. This may not reflect clinical practice given that non-severe relapses are likely to be common and could be treated with GC. This assumption may bias in favour of avacopan given that patients transition into the Relapse health state more frequently in the comparator arm and relapse is associated with higher costs and poorer outcomes.

6.45 Newly diagnosed patients and relapsing patients (those with worsening disease after having previously achieved remission on other treatments) entering the model were treated the same in the model with the same transition probabilities. ADVOCATE trial subgroup analyses on newly diagnosed vs relapsed patients indicated differences in the proportions of patients achieving remission at Weeks 26 and 52 (Table 6). These differences have a substantial impact on the ICER. Sensitivity analyses conducted during the evaluation showed that the ICER for only newly diagnosed AAV patients was $155,000 to < $255,000/QALY gained (169% increase from base case of $55,000 to < $75,000/QALY gained) and for only relapsed patients was $25,000 to < $35,000/QALY gained (63% decrease from base case). The PSCR argued that, consistent with the restriction which does not limit use by AAV subtype or newly diagnosed/relapsed patients, the severe AAV cohort should be modelled as a whole based on the ITT population from ADVOCATE. The ESC considered that even if a decision is based on the full cohort, there were substantial differences in effectiveness and subsequent cost-effectiveness for patient subtypes. The ESC considered the current approach obscures these differences. The pre-PBAC response reiterated that the ADVOCATE trial was not powered to consider differences in GPA/MPA cohorts, relapsed/newly diagnosed or any subgroups.

6.46 Similarly, the treatment effect for GPA and MPA patients was assumed to be the same. Subgroup analyses by AAV type indicate differences in remission rates at Weeks 26 and 52 with results driven by a larger treatment effect for MPA patients (Table 6) who likely make up a smaller proportion of AAV patients in the Australian setting.

6.47 The model assumed that patients would be treated with avacopan over 24 months (6 months of induction, followed by 18 months of maintenance). The model also allowed patients in remission to be re-inducted with avacopan up to two times. There is currently no evidence to support the use of avacopan beyond 52 weeks, as maintenance therapy. Similarly, there is no evidence to support the use of avacopan for multiple inductions. The PSCR argued that clinicians present at the sponsors October 2022 Advisory Board Meeting indicated it would be clinically inappropriate to limit treatment to 52-weeks if a patient has exhibited a positive response to treatment simply because the clinical trial data extends only to 52 weeks. The ESC reiterated

concerns that the difference in the proportion of patients achieving sustained remission between the two treatment arms (see paragraph 6.21) was driven by those who were not on any maintenance therapy after rituximab (see paragraph 6.26).

6.48 The duration of the time horizon (30 years) is long relative to the ADVOCATE trial duration of 52 weeks. The PSCR argued that treatment with avacopan will have lasting impacts on renal disease progression and mortality which can only be appropriately captured with a 30-year time horizon. The ESC noted the sensitivity analysis presented in Table 15 shows that the ICER is sensitive to the time horizon selected. The ESC considered the modelled effectiveness of avacopan is perpetuated over a long time horizon, biasing in favour of avacopan. The ESC noted that the mortality benefit is built into the model a priori. The ESC considered the modelled difference in mortality was not supported by the clinical evidence and appeared to be mainly driven by increased deaths due to infections from GC in the SOC arm (see paragraph 6.63).

Transition probabilities

6.49 The remission and relapse rates and transition probabilities applied in the model were based on proportions of patients in remission at Weeks 26 and 52 from the ADVOCATE trial, although it is noted that the model validation outputs show that remission at 52 weeks is overestimated. There is uncertainty in the comparative effectiveness of avacopan + SOC versus prednisolone + SOC given that patients in the avacopan + SOC arm were treated with higher mean non-study supplied GCs dose. This could confound part of the treatment effect for avacopan + SOC, by masking a delayed or less potent treatment effect of avacopan + SOC leading to uncertainty in the treatment effect modelled.

6.50 The submission assumed that the treatment effect for the first induction is the same as that for subsequent re-inductions. While avacopan appeared to have more favourable sustained remission rates among relapsed patients at 52 weeks, it remains uncertain if subsequent inductions with avacopan would result in the same treatment effect.

6.51 The model assumed that the probability of moving from Remission to Relapse health states decreases with time, with an increased risk in the first two years from remission. To account for this, the transition probability from Remission to Relapse after two years in remission was assumed to be 1/5 (20% reduction) of the transition probability in the first two years. While a reduced risk of relapse over time after remission is plausible, there is uncertainty in the magnitude of reduction. It is noted that this assumption similarly applies to both the intervention and comparator arms. The ICER is sensitive to this assumption. Applying 10% and 30% reductions changes the ICER from $55,000 to < $75,000/QALY gained to $55,000 to < $75,000/QALY gained (14% decrease from base case) and $75,000 to < $95,000/QALY gained (14% increase) respectively.

6.52 The economic model incorporated eGFR data reported from the ADVOCATE trial to estimate the risk of ESRD for patients on avacopan + SOC and prednisolone + SOC.

Improvements in eGFR as reported in the trial were converted into the corresponding change in ESRD risk using the hazard ratio (HR) (0.90; 95% CI, 0.86, 0.95) reported in Gercik et al. (2020) for ESRD per mL/min change in eGFR from baseline. There is uncertainty in the assumptions made in estimating the transition probabilities for ESRD because:

- There may be selection bias for the eGFR outcomes presented in the ADVOCATE trial as patients without renal disease at baseline were excluded from analysis of this outcome. Absolute eGFR improvement was greater among patients with lower baseline eGFR. As such, improvements in eGFR may have been overestimated, favouring avacopan. The PSCR argued that improvement in eGFR from patients was based on all patients with renal activity and eGFR measurement at baseline, which accounted for over 80% of patients in ADVOCATE. The ESC noted that change from baseline in eGFR, was measured in subjects with renal disease based on the BVAS renal component. The ESC noted that just under 20% of the ITT population did not meet the renal disease criteria and were excluded from the analysis of this outcome.
- Although the differences in eGFR recovery at Weeks 26 and 52 between the avacopan + SOC and prednisolone + SOC arms from the ADVOCATE trial were statistically significant, the 95% CIs were wide. For example, at Week 26 the 95% CI for eGFR recovery was 0.1 to 5.8mL/min. The difference is maintained and compounded over subsequent relapses in the economic model which favours the avacopan + SOC arm.
- The HR of 0.90 from Gercik et al. (2020) was among the lowest HRs reported across available studies. A pooled estimated of 0.955 from Brix et al., Gercik et al. and Ford et al. was recommended by NICE (NICE avacopan HTA, 2022). Applying a HR of 0.955 (pooled estimate) changed the ICER from $55,000 to < $75,000/QALY gained to $75,000 to < $95,000/QALY gained (20% increase).
- These assumptions and changes in eGFR drive the risk of ESRD (particularly for the prednisolone + SOC arm) and have considerable impact on the ICER given that ESRD is an expensive health state.

6.53 The submission assumed each subsequent relapse was associated with a 10 mL/min decrease in eGFR based on advice from clinical experts and data from Slot et al. (2003). The magnitude of eGFR decrement applied is uncertain because of the variance (large standard deviation) in the observed data from Slot et al. (2003). Halving the assumed eGFR decrease associated with relapse changed the ICER from $55,000 to < $75,000/QALY gained to $75,000 to < $95,000/QALY gained (14% increase) and removing this effect (assuming no decrement) changes the ICER to $75,000 to < $95,000/QALY gained (33% increase). The PSCR argued that clinicians considered a decline of 10 mL/min to be at the lower end typically observed upon relapse. When a 20 mL/min decrease in eGFR is assumed, the ICER decreased to $55,000 to < $75,000/QALY. The ESC considered the ICER is very sensitive to the

assumed change in eGFR at relapse as it drives the utilities and costs when ESRD is reached. Separately, the ESC noted that Appendix 1 of the PBAC Guidelines, version 5, details how expert opinion can be incorporated into PBAC submissions and considered that the information from on the clinicians referred to the by PSCR was not provided.

6.54 To reflect the reduced burden of infection-related deaths resulting from the GC sparing due to avacopan use, the model incorporated a morality risk due to increased risk of infection related to GC use using the reported incidence of GC-related adverse events from the ADVOCATE trial (1.8% in avacopan + SOC and 6.7% in prednisolone + SOC). Data from the ADVOCATE trial only reported proportions therefore, the significance of this difference is unclear. Furthermore, the trial data does not support the impact of this outcome on mortality. The model assumed half of deaths in the first year in AAV are attributed to infections and 73.1% of infections were avoided due to avacopan use. The ICER is sensitive to this parameter. Removing this mortality risk changed ICER changed from $55,000 to < $75,000/QALY (base case) to $75,000 to < $85,000/QALY (17% increase).

Extrapolation

6.55 The treatment effect of avacopan was assumed to wane linearly over one year to match the prednisolone + SOC following the cessation of avacopan. There are limited data on treatment effect waning as the follow-up period without avacopan treatment in the ADVOCATE trial was 56 days (8 weeks). Within this 8-week period, it was reported that 6 subjects (3.8%) in the avacopan + SOC and 7 subjects (4.5%) in the prednisolone + SOC relapsed. The method of extrapolating treatment effectiveness beyond the study period is highly uncertain. The base case ICER changed from $55,000 to < $75,000/QALY gained to $95,000 to < $115,000/QALY gained when the treatment effect was turned off after 52 weeks. When treatment effect waned after 6 months of stopping avacopan (instead of 52 weeks base case), the ICER was $75,000 to < $95,000/QALY gained (16% increase from base case). The PSCR argued that the efficacy of avacopan compared with prednisolone was maintained following the 8-week follow-up period after cessation of avacopan. The ESC considered the data from the 8-week follow-up period was unlikely to robustly inform a 12 month waning period and noted this had a substantial effect on the ICER.

Utility values

6.56 The model applied utility values from EQ-5D-5L data from the ADVOCATE trial stratified by health state (Active disease, Remission and Relapse) according to remission and relapse definitions of the ADVOCATE trial. Pooled utility values across the two study arms were applied. This is reasonable and the use of non-treatment specific health state values represents a conservative approach.

6.57 The utility values applied in the model for dialysis and transplant were 0.443 and 0.712, respectively. An alternative source for utility values from a systematic review and meta-analysis (Wyld et al. 2012) reported a utility value of 0.70 (95% CI, 0.62-0.78)

among patients on dialysis and 0.82 (95% CI, 0.74, 0.90) among patients with transplant. The ICER is sensitive to these ESRD utility values. Revising the utility values for both the transplant and dialysis health states changed the ICER from $55,000 to < $75,000/QALY at base case to $75,000 to < $95,000/QALY (21% increase).

6.58 The submission applied an assumed decrement of 0.1 for the occurrence of any GC-related infections. This parameter was tested in sensitivity analysis during the evaluation, and it did not appear to have any substantial impact the ICER.

Costs

6.59 The model incorporated treatment costs relevant to both induction and maintenance therapies which included avacopan and recommended concomitant medications. Costs related to resource use for monitoring of the disease, and hospitalisation and clinic visits to cover serious adverse events including infections were included and were informed by the Australian Vasculitis Advisory Board and an unpublished draft manuscript from Monash Health Vasculitis Clinic. Hospitalisation data reporting average number of hospitalisations and length of stay were available from the ADVOCATE trial but were not described in the submission. The model did provide an option to include hospitalisation data from ADVOCATE and this was presented in a sensitivity analysis in the submission. Including this option changed the ICER from $55,000 to < $75,000/QALY gained at base case to $75,000 to < $95,000/QALY gained (18% increase).

6.60 The costs related to ESRD treatment were estimated based on the treatment options available to ESRD patients. The cost for the ESRD health state was calculated based on cost of the treatment options including dialysis, transplant and conservative management (NSW Dialysis Costing Study conducted in 2008) and the proportion of ESRD patients for each of the options (annual report of ANZDATA 2020). This appears to be a similar approach applied in the chronic kidney disease model for a previous PBAC submission for dapagliflozin in CKD. At that time, the ESC noted that there was substantial uncertainty in the approach of estimating ESRD costs due to the assumed fixed distribution of patients among ESRD treatment modalities (17.4% conservative management, 43.0% dialysis, 39.6% transplant), and the use of unit costs based on inflation of older data that may not reflect current costs in clinical practice (para 6.47, dapagliflozin, Public Summary Document, September (addendum) 2021 PBAC meeting). Similar issues are present for this economic evaluation resulting in high uncertainty in the cost estimates used.

6.61 Overall, the observed costs applied for the ESRD-related treatments appear to be high for the following reasons:

- The submission applied a constant cost for each year of the model (more reflective of first year costs) in its estimations thus may have overestimated dialysis and transplant costs for subsequent years.

- The source used (report from Deloitte Access Economics, 2011) to estimate the cost of conservative management may be overestimated because they include costs beyond those that are relevant to the healthcare system perspective (i.e., included patient transport, aids and appliances, health research and administration systems).

This is important because cost offsets were largely driven by costs in the ESRD health state.

6.62 Compared with the results observed in the ADVOCATE trial, the proportions of patients in the Remission health state in the economic model were lower at Week 26 and higher at Week 52. The evaluation considered this will favour avacopan given the 30-year time horizon.

6.63 Based on the validation checks presented in the submission, there is an observed difference in mortality between the avacopan + SOC and prednisolone + SOC arms (of up to 15% in Year 15). This is not supported by clinical evidence as mortality was not assessed in the ADVOCATE trial and follow up was only up to 1 year. Mortality appears to be mainly driven by deaths due to infections avoided through use of avacopan. The submission applied a relative risk reduction in infections of 73.1% based on reported incidence of serious adverse events considered related to prednisone from the ADVOCATE trial. Turning off this mortality adjustment (i.e., no deaths due to infections avoided by avacopan) changed the ICER from $55,000 to < $75,000/QALY (base case) to $75,000 to < $95,000/QALY (17% increase).

6.64 Compared to the survival estimates from the literature, survival is likely overestimated in the model. With more patients surviving this means that in absolute terms there would be more patients available to transition into other health states. For example, treatment with avacopan was assumed to result in an improvement in eGFR, therefore comparatively more patients in the prednisolone + SOC arm compared to the avacopan + SOC arm would transition into the ESRD health state (which has higher costs and poorer outcomes). As such, higher survival (with more patients remaining alive in the model) is likely to favour avacopan.

6.65 The disaggregated costs for comparison of avacopan with GC are presented in Table 11. The model resulted in an incremental cost of $ which was driven by the cost of avacopan treatment in the Remission health state and largely offset by resource use in the ESDR health state.

Table 11: Disaggregated summary of costs by health states and resource use

Health state	Resource use by health state	Avacopan + SOC cost	GC + SOC cost	Incremental cost	% of total incremental cost
Active disease	Drug cost	$	$1,931	$	
	Resource use	$5,144	$5,624	-$480	-1%
	Total	$	$7,555	$	
Remission	Drug cost	$	$1,218	$	
	Resource use	$32,535	$27,551	$4,985	8%
	Total	$	$28,769	$	
Relapse	Drug cost	$	$3,160	$	
	Resource use	$24,871	$34,706	-$9,835	-16%
	Total	$	$37,865	$	
ESRD	Drug cost	$0	$0	$0	0%
	Resource use	$111,305	$170,449	-$59,144	-97%
	Total	$111,305	$170,449	-$59,144	-97%
Death	Drug cost	$0	$0	$0	0%
	Resource use	$3,523	$3,791	-$268	0%
	Total	$3,523	$3,791	-$268	0%
Total		$	$248,429	$	100%

Source: Compiled during the evaluation using data from 'Engine AVA+CYC' and 'Engine CYC + GC' tabs of the model (Attachment 14)
Abbreviations: ESRD, end stage renal disease; GC, glucocorticoid; SOC, standard of care.
Note: There is a slight discrepancy (of a few dollars) in the total costs presented in this table compared to Table 14.

6.66 The disaggregated health outcomes for comparison of avacopan with GC are presented in Table 12. The main driver of the incremental outcomes was QALYs gained in the Remission health state and offsets were driven by the ESRD health state.

Table 12: Disaggregated summary of health outcomes by health states

Outcome/Health state	Outcome for avacopan + SOC	Outcome for GC + SOC	Incremental outcome	% of total incremental outcome
QALYs				
Active disease	0.19	0.20	0.00	0%
Remission	4.98	3.33	1.65	189%
Relapse	0.77	1.01	-0.24	-28%
ESRD	1.15	1.78	-0.63	-72%
Adverse events	-0.39	-0.48	0.09	11%
Total	6.70	5.83	0.87	100%

Source: Compiled during the evaluation using data from 'Engine AVA+CYC' and 'Engine CYC + GC' tabs of the model (Attachment 14)
Abbreviations: ESRD, end stage renal disease; GC, glucocorticoid; SOC, standard of care.

6.67 Table 13 summarises the key drivers of the model.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Time horizon	30 years.	Very high, favours avacopan. Use of a 10- and 15-year time horizon increased the ICER to $[redacted][2] and $[redacted][3]/QALY gained respectively.
Patient subgroups	The same transition probabilities were applied for newly diagnosed or relapsed populations and for each AAV type (GPA or MPA)	Very high, could favour either avacopan or comparator depending on the treatment effect observed and the distribution of these subgroups in the Australian population.
Extrapolation	Treatment effect continued for 12 months following cessation of avacopan treatment.	High, favours avacopan. ICER increased to $[redacted][3]/QALY gained when the treatment effect was stopped upon avacopan cessation).
Re-inductions with avacopan	Two re-inductions allowed over the course of a patient's lifetime	High, favours avacopan. When no re-inductions were allowed, the ICER increased to $[redacted][3]/QALY gained.
HR applied to corresponding change to eGRF	HR=0.90 from Gercik et al. (2020)	High, favours avacopan. Using HR=0.955 (pooled estimate from Brix et al., Gercik et al. and Ford et al.), the ICER increased to $[redacted][4]/QALY gained.
Utility values	0.458 and 0.712 for dialysis and transplant respectively	High, favours avacopan. Using corresponding values from Wyld et al. (2012): 0.70 and 0.82 increased the ICER to $[redacted][4]/QALY.

Source: Compiled during the evaluation using information from Table 3-20, p127-128 of the submission and outputs from Attachment 14
Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody associated vasculitis; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MPA, microscopic polyangiitis; QALY, quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$155,000 to < $255,000*
[3] *$95,000 to < $115,000*
[4] *$75,000 to < $95,000*

6.68 Table 14 presents the results of the economic evaluation. A trial-based evaluation based on outcomes from the ADVOCATE trial was conducted during the evaluation.

Table 14: Results of the stepped economic evaluation

Step and component	Avacopan + SOC	GC + SOC	Increment
Step 1: Trial-based analysis (26 weeks, drug costs only, no discounting)			
Costs	$	$2,623	$
Proportion of patients at disease remission	72.3	70.1	3.4 (NS)
Incremental cost/extra patient at disease remission			**Not reported [a]**
Step 2: Trial-based analysis (52 weeks, drug costs only, no discounting)			
Costs	$	$3,644	$
Proportion of patients at sustained remission	65.7	54.9	12.5
Incremental cost/extra patient at sustained remission			**$** [1]
Step 1a: Model-based analysis (26 weeks, drug costs only, no discounting)			
Costs	$	$2,623	$
QALYs	0.30	0.29	0.01
Incremental cost/QALY gained			**$** [2]
Step 2a: Model-based analysis (52 weeks, drug costs only, no discounting)			
Costs	$	$3,644	$
QALY	0.62	0.60	0.02
Incremental cost/QALY gained			**$** [2]
Step 3a: Model-based analysis (5 years, drug costs only, duration of therapy 12 months, no avacopan reinductions, no treatment effect after 52 weeks)			
Costs	$	$3,887	$
QALY	2.56	2.49	0.070
Incremental cost/QALY gained			**$** [3]
Step 3b: Model-based analysis (5 years, drug costs only, duration of therapy 12 months, no avacopan reinductions, treatment effect wanes over 1 year after stopping avacopan)			
Costs	$	$3,887	$
QALY	2.60	2.49	0.113
Incremental cost/QALY gained			**$** [4]
Step 3c: Model-based analysis (5 years, drug + health state + event costs, duration of therapy 12 months, no avacopan reinductions, treatment effect wanes over 1 year after stopping avacopan)			
Costs	$	$104,549	$
QALY	2.60	2.49	0.113
Incremental cost/QALY gained			**$** [5]
Step 4: Model-based analysis (30 years – base case, outcome in life years)			
Costs	$	$248,431	$
Lys	9.72	8.50	1.23
Incremental cost/extra LY gained (base case)			**$** [6]
Step 5: Model-based analysis (30 years – base case)			
Costs	$	$248,431	$
QALYs	6.70	5.83	0.87
Incremental cost/extra QALY gained (base case)			**$** [b,7]

Source: Compiled during the evaluation using output generated from Attachment 14

Abbreviations: GC, glucocorticoid; ICER, incremental cost-effectiveness ratio; LY, life year; NS, not statistically significant; QALY, quality-adjusted life year; SOC, standard of care

[a] The ICER is not reported. Outcome for avacopan at Week 26 did not demonstrate superiority.

[b] The ICER was updated by the Sponsor from $55,000 to < $75,000 to $55,000 to < $75,000/QALY gained following correspondence to correct transplant cost during the evaluation (CORR021679 – Avacopan PBAC submission – Request for further information, dated 31st March 2023).. Given the small impact of the correction, data as presented in the original economic model (Attachment 14) are used in throughout the ESC advice.

The redacted values correspond to the following ranges:

[1] *$5,000 to < $15,000*

[2] *> $1,055,000*

[3] *$555,000 to < $655,000*

[4] *$355,000 to < $345,000*
[5] *$255,000 to < $355,000*
[6] *$45,000 to < $55,000*
[7] *$55,000 to < $75,000*

6.69 The results of key univariate sensitivity analyses are summarised in Table 15. In addition to the time horizon, in sensitivity analyses conducted during the evaluation the results were most sensitive to alternative values for the treatment effect taken from ADVOCATE subgroup analyses.

Table 15: Sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change in ICER
Base case	[redacted]	**0.87**	[redacted][1]	
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	[redacted]	1.670	[redacted][2]	-53%
• 3.5% costs and outcomes	[redacted]	1.047	[redacted][1]	-19%
Time horizon (base case 30 years)				
• 10 years	[redacted]	0.387	[redacted][3]	142%
• 15 years*	[redacted]	0.593	[redacted][4]	42%
• 20 years	[redacted]	0.756	[redacted][5]	12%
Subgroup analysis*				
Disease status				
• Newly diagnosed patients	[redacted]	0.418	[redacted][3]	169%
• Relapsed patients	[redacted]	1.534	[redacted][6]	-63%
AAV type				
• GPA	[redacted]	0.448	[redacted][3]	187%
• MPA	[redacted]	1.357	[redacted][2]	-70%
Treatment effect after treatment cessation (base case linear waning after 1 year)				
• No effect upon stopping avacopan	[redacted]	0.731	[redacted][4]	42%
• Wane after 6 months	[redacted]	0.813	[redacted][5]	16%
• Wane after 2 years	[redacted]	0.919	[redacted][1]	-11%
HR applied to corresponding change to eGRF (base case HR=0.90 from Gercik et al. (2020))				
• HR=0.96 from Brix et al. (2018)	[redacted]	0.772	[redacted][5]	22%
• HR=0.955 from pooled estimate from Brix et al., Gercik et al. and Ford et al.) * [a]	[redacted]	0.782	[redacted][5]	20%
Utility values for dialysis and transplant (base case 0.458 and 0.712 respectively)*				
• Values from Wyld et al. (2012): 0.70 and 0.82	[redacted]	0.719	[redacted][5]	21%
ESRD health state cost (base case $3,774)*				
• + 20%	[redacted]	0.872	[redacted][1]	-19%

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change in ICER
• - 20%	[redacted]	0.872	[redacted][5]	19%
eGRF decrement associated with relapse (base case 10 mL/min decrease)				
• 5 mL/min decrease	[redacted]	0.827	[redacted][5]	14%
• 20 mL/min decrease	[redacted]	0.826	[redacted][1]	-7%
• No decrease with relapse	[redacted]	0.752	[redacted][5]	33%
Treatment duration (base case 6 months induction + 18 months maintenance and 2 reinductions)				
• 6 months induction + 6 months maintenance and no avacopan reinductions (as per ADVOCATE trial)	[redacted]	0.274	[redacted][1]	-9%
• 6 months induction + 12 months maintenance and 2 reinductions	[redacted]	0.724	[redacted][5]	20%
Number of reinductions with avacopan (base case 2)				
• No reinductions	[redacted]	0.394	[redacted][4]	39%

Source: Table 3-20, p127-128 of the submission and added to during the evaluation (*)
Abbreviations: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GPA, granulomatosis with polyangiitis; HR, hazard ratio; ICER; incremental cost-effectiveness ratio; MPA, microscopic polyangiitis; QALY, quality-adjusted life year.
[a] As recommended by NICE
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000
[2] $25,000 to < $35,000
[3] $155,000 to < $255,000
[4] $95,000 to < $115,000
[5] $75,000 to < $95,000
[6] $15,000 to < $25,000

Drug/cost/patient/year

6.70 The avacopan drug cost per year was $[redacted] per patient based on the proposed effective DPMQ price of $[redacted] (10 mg, 180 capsules) per script and 10.4 scripts per patient per year, assuming 86.4% compliance.

6.71 A comparison of avacopan use between trial setting, the economic model and the financial estimates is presented in Table 16. The costs applied in the economic analysis and financial estimates were similar. The main differences were the assumptions relating to the duration of treatment and number of avacopan re-inductions which were inconsistently applied for the economic analysis and financial estimates. The submission did not provide a justification for this.

Table 16: Drug cost per patient per year for avacopan

	Trial dose and duration	Model	Financial estimates
Proposed regimen	30 mg twice daily for 12 months	30 mg twice daily for 6 months (induction) followed by 18 months (maintenance)	30 mg twice daily for at least 12 months [a]
Avacopan re-induction	No	2	Unlimited
Mean total duration of treatment	305.1 days (10.0 months)	25.8 months [b]	13.8 months [c]
Mean dose	60.2 mg/day	60 mg/day	60 mg/day
Compliance	86.4%	86.4%	86.4%
Cost/patient/month [d]	$	$ [e]	$
Cost/patient/year [d]	$	$	$

Source: Table 2-15, p66, 126 of the submission and from outputs sourced from Attachment 14 and 16

[a] This is unclear as not clearly described in the submission

[b] Estimated by the submission. It is unclear how this was derived.

[c] Duration of treatment varied depending on the population: 14.21 months (newly diagnosed & relapsed), 12.46 months (re-induction), 7.15 months (grandfathered)

[d] Adjusted for compliance of 86.4% as reported in the ADVOCATE trial (approximates 10.4 scripts per year)

[e] Re-calculated from $ per cycle from the economic model (Attachment 14)

Estimated PBS usage & financial implications

6.72 The submission was considered by DUSC.

6.73 The submission used an epidemiological approach to estimate the financial implications associated with the proposed listing of avacopan. The submission identified four patient populations that would be eligible for avacopan: (1) newly diagnosed, (2) relapsed, (3) re-induction and (4) grandfathered patients. Eligible patients were estimated based on the incidence and prevalence of GPA and MPA patients (for Populations 1, 2 and 3) and based on the Sponsor's compassionate program for Population 4.

6.74 Table 17 summarises the key inputs and issues for financial estimates.

Table 17: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Population 1: Eligible newly diagnosed patients			
Incident GPA and MPA patients	Yr 1: 283 Yr 2: 287 Yr 3: 291 Yr 4: 296 Yr 5: 300 Yr 6: 304	Ormerod et al. (2008)	The reported 95% CI of incidence estimates were wide, between 3.5 and 15.8 per million for GPA and between 1.6 and 11.7 per million for MPA. There also appears to be variations in estimates across the different sources/regions of Australia. Therefore, the incidence estimates are highly uncertain. The financial estimates are highly sensitive to incidence which determines the number of patients eligible for avacopan. DUSC agreed with the evaluation that the incidence estimates are uncertain however noted that they align with previous PBS utilisation of rituximab for severe active GPA/MPA between 2016 to 2022. DUSC considered that the inputs derived from Ormerod et al. (2008) are likely appropriate given this alignment.
Proportion with severe disease	87.8%	Rutherford et al. (2018)	The source of the disease severity parameter was a study published as an abstract and there was limited information to assess the validity of the value. An alternative approach could be to assume that all patients from Ormerod et al (2008) are severe (i.e., 100%) given the patients in the study required

Data	Value	Source	Comment
			hospital (specialist) care. DUSC agreed with the evaluation and considered that it would be appropriate for 100% of patients to be assumed to have severe disease.
Population 2: Eligible relapsed patients			
Prevalent GPA and MPA patients	Yr 1: 2,827 Yr 2: 2,871 Yr 3: 2,916 Yr 4: 2,960 Yr 5: 3,003 Yr 6: 3,046	Ormerod et al. (2008)	The reported 95% CI of prevalence estimates were wide, between 76.9 and 116.1 per million for GPA and between 27.7 and 53.3 per million for MPA. There also appears to be variations in estimates across the different sources/regions of Australia. Therefore, the prevalence estimates are highly uncertain. The financial estimates are highly sensitive to this parameter as this will determine the number of patients eligible for avacopan. DUSC considered that the inputs derived from Ormerod et al. (2008) are likely appropriate given their alignment with previous rituximab utilisation
Proportion with severe disease	70%	Global Blood Therapeutics	It is unclear what this source was, and a reference was not provided with the submission. An alternative approach could be to assume that the estimated population from Ormerod et al (2008) are all severe. DUSC agreed with the evaluation.
Relapse rate	10%	Rituximab PSD (March 2015 PBAC meeting)	It appears that DUSC had previously considered 25% in Year 1 and 10% for subsequent years to be a reasonable assumption (paragraph 6.27, rituximab, Public Summary Document, March 2015 PBAC meeting). DUSC considered the relapse rate to be appropriate.
Population 3: Eligible for avacopan reinduction			
Relapse rate	18% after 1st induction and 5% for subsequent inductions	Rates from the economic model (Section 3.4)	This appears to be based on proportion of patients in remission at 26 and 52 weeks as per the ADVOCATE trial and based on submission's assumptions. A relapse rate of 10% was used for Population 2, which is inconsistent with Population 3 as both relate to relapsing patients. DUSC considered Population 3 to be inadequately defined with a poorly justified relapse rate that differed from Population 2. DUSC considered that removing this population would remove a substantial amount of uncertainty from the model.
Proportion of patients receiving avacopan induction	100%	Assumption	Reasonable if re-induction with avacopan is deemed appropriate. As per comment above, DUSC considered that removing this population would remove a substantial amount of uncertainty in the model.
Population 4: Grandfathered patients			
Estimated patient numbers	Yr 1: [redacted][1] Not applicable to subsequent years	Based on Sponsor's compassionate program	Given that prevalence data were used to estimate the number of eligible relapsed patients, grandfathered patients are already included in estimates above. This would lead to overestimation of patients eligible for avacopan. DUSC agreed with the evaluation and noted that these patients would have been counted from the prevalent pool.
Treatment utilisation			
Uptake rate	Yr 1: 50% Yr 2: 50% Yr 3: 80% Yr 4: 85% Yr 5: 90%	Assumption based on clinical guidance	Given that avacopan is the first-in-class treatment with effectiveness and safety data up to 52 weeks, it is reasonable to assume uptake to be slow in the first few years. However, there is uncertainty in the magnitude of the uptake rate. The financial estimates are highly sensitive to this assumption given that the

Data	Value	Source	Comment
	Yr 6: 90%		cost of avacopan is the key driver of the financial estimates. DUSC considered the uptake rates to be appropriate if Population 3 is removed from the model. DUSC noted that the higher uptake rates would lead to utilisation numbers mirroring rituximab use and also account for reinduction. DUSC considered that the uptake rate in Year 2 could be increased to 65% to resemble the rituximab trajectory more closely.
Duration of treatment	14.21 months (newly diagnosed & relapsed), 12.46 months (re-induction), 7.15 months (grandfathered)	Assumption	Patients in the ADVOCATE trial were treated with avacopan over a 52-week period and the mean duration of exposure to avacopan in the ADVOCATE trial was 305.1 days (10 months) (Table 2-15, p66 of the submission). This was inconsistent with the duration of therapy of 6-months induction followed by an 18-month maintenance treatment applied in the economic model. The PSCR stated that the average duration of treatment in section 4 is the same as in the economic model but takes into account patients withdrawing early due to relapse/ disease progression/ death. DUSC considered this treatment duration to be appropriate. DUSC considered that the assumption of no more than two reinductions used by the economic model compared to unlimited reinductions in section 4 would have minimal impact as it is unlikely for any major use beyond two reinductions. DUSC considered that availability beyond two reinductions would be important for the few patients who would need to access it.
Avacopan compliance	86.4% (estimated 10.5 scripts per year)	ADVOCATE trial	DUSC agreed with the evaluation that this is appropriate.
Costs			
Proposed medicine (avacopan)	$[redacted] [a]	Requested (effective) price	
Comparator (prednisone)	1 mg: $15.38 [a] 5 mg: $15.76 [a] 25 mg: $16.59 [a]	PBS item numbers: 1934T, 1935W, 1936X	

Source: Compiled during the evaluation based on information sourced from Section 4.1, 4.2 and 4.3 of the submission
Abbreviation: CI, confidence interval; DUSC; Drug Utilisation Sub Committee; GPA, granulomatosis polyangiitis; MPA, microscopic polyangiitis; PBS, Pharmaceutical Benefits Scheme; PBAC, Pharmaceutical Benefits Advisory Committee; Yr, year; PSD, Public Summary Document.
[a] DPMQ prices
The redacted values correspond to the following ranges:
[1] < 500

6.75 There is inconsistency in the submission's approach to the requested PBS listing for maintenance of remission. The requested listing requires patients to have responded to avacopan defined as BVAS score of 0 (i.e., be in remission) for continued access to avacopan. The submission's approach assumed that all inducted patients would go on to receive maintenance treatment. This may overestimate the use of avacopan given that at 6 months, only 72.3% and 70.1% of patients in the avacopan + SOC and GC + SOC arms achieved remission at 26 weeks in the ADVOCATE trial.

6.76 The submission stated that prednisone is expected to be replaced by the proposed listing of avacopan. While avacopan is expected to replace the use of prednisone to reduce GC-related toxicities, in practice, it is unlikely to completely replace prednisone. In the ADVOCATE trial non-study supplied GC use was slightly higher in the avacopan arm compared to the GC + SOC arm. As such, the approach by the submission may have overestimated the changes in use of prednisone. This will likely only have a minor impact due to the small cost of prednisone relative to avacopan.

6.77 Table 18 summarises the estimated eligible population, and the net cost to PBS/RPBS of listing avacopan, based on the submission's DPMQ of $ (effective price).

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[1]	[1]	[1]	[1]	[1]	[1]
Number of patient years of treatment [a]	[1]	[1]	[1]	[1]	[1]	[1]
Number of scripts dispensed [b]	[2]	[2]	[2]	[2]	[3]	[3]
Estimated financial implications of avacopan						
Cost to PBS/RPBS less copayments ($)	[4]	[4]	[5]	[5]	[5]	[5]
Estimated financial implications for prednisone						
Cost to PBS/RPBS less copayments ($)	[6]	[6]	[6]	[6]	[6]	[6]
Net financial implications						
Net cost to PBS/RPBS ($)	[4]	[4]	[5]	[5]	[5]	[5]

Source: Tables 4-2, 4-4, 4-5, 4-8, 4-12, 4-14 and 4-15, p133-139 of the submission

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Schedule of Pharmaceutical Benefits.

[a] Duration of treatment: 14.21 months (newly diagnosed & relapsed), 12.46 months (re-induction), 7.15 months (grandfathered)

[b] Assuming 10.5 per year as estimated by the submission.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *5,000 to < 10,000*

[4] *$10 million to < $20 million*

[5] *$20 million to < $30 million*

[6] *net cost saving*

6.78 The total cost to the PBS/RPBS of listing avacopan was estimated to be $10 million to < $20 million in Year 1 and $20 million to < $30 million in Year 6, totalling $100 million to < $200 million over 6 years. The impact of offsets due to prednisone were small relative to the cost of avacopan.

6.79 The submission stated that < 500 patients were expected to be grandfathered based on the Sponsor's compassionate program. Given that prevalence data were used, grandfathered patients are already included, therefore have been double counted. Sensitivity analysis conducted during the evaluation excluding grandfathered patients from the financial estimated had a small impact on the total net cost to PBS/RPBS over 6 years (1% decrease).

6.80 DUSC considered the estimates presented in the submission to be reasonable. The main issues identified were:

- DUSC noted that the estimated use of avacopan was aligned with the previous use of rituximab for the same indications between 2016-2022 and that avacopan was unlikely to grow the population.
- DUSC considered Population 3 (patients eligible for avacopan reinduction) to be inadequately defined, with a poorly justified relapse rate that differed from Population 2 (relapsed patients). DUSC considered that deleting this population would remove a substantial amount of uncertainty from the model.
- DUSC considered that the availability of use beyond two reinductions would be clinically important but would have a minimal impact to the financial estimates, as few patients are likely to require it.

6.81 The results of the sensitivity analysis conducted during the evaluation are presented in Table 19. The results are most sensitivity to the incidence and prevalence estimates used.

Table 19: Results of sensitivity analysis conducted during the evaluation

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total over 6 years	% change
Base case								
Net cost to PBS/RBS ($)	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3	
Using lower 95% CI values for incident and prevalence estimates from Ormerod et al. (2008)								
Net cost to PBS/RBS ($)	[redacted]4	[redacted]4	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]5	-43%
Using upper 95% CI values for incident and prevalence estimates from Ormerod et al. (2008)								
Net cost to PBS/RBS ($)	[redacted]2	[redacted]2	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]7	68%
Proportion of severity of disease is set to 100% for incident and prevalent patients								
Net cost to PBS/RBS ($)	[redacted]1	[redacted]2	[redacted]2	[redacted]8	[redacted]8	[redacted]8	[redacted]3	20%
Relapse rate at 25% in Year 1 and 10% for subsequent years (for Population 2)								
Net cost to PBS/RBS ($)	[redacted]2	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3	7%
Reduce uptake rate by 10% across all years								
Net cost to PBS/RBS ($)	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3	-12%
Uptake rate of 50% across all years								
Net cost to PBS/RBS ($)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]9	-29%
Excluding grandfathered patients								
Net cost to PBS/RBS ($)	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3	-1%

Source: Conducted during the evaluation

Abbreviations: CI, confidence interval; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Schedule of Pharmaceutical Benefits

The redacted values correspond to the following ranges:

[1] $10 million to < $20 million
[2] $20 million to < $30 million
[3] $100 million to < $200 million
[4] $0 to < $10 million
[5] $80 million to < $90 million
[6] $40 million to < $50 million
[7] $200 million to < $300 million
[8] $30 million to < $40 million
[9] $90 million to < $100 million

Quality Use of Medicines

6.82 DUSC noted that the submission did not present any quality use of medicines (QUM) initiatives. DUSC considered that, while these patients would have follow up from specialist physicians for their disease and exposure to other immunosuppression, it was inappropriate for a medication with a novel mechanism of action and limited long-term safety data to be provided without any planned training of health practitioners and patients or adverse event surveillance programs.

Financial Management – Risk Sharing Arrangements

6.83 No risk sharing arrangements were proposed in the submission.

For more detail on PBAC's view, see section 7 PBAC Outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing for avacopan for the treatment of severe active granulomatosis with polyangiitis (GPA) or severe active microscopic polyangiitis (MPA) in combination with rituximab or cyclophosphamide/azathioprine. The PBAC acknowledged there was a clinical need for treatments that can be used to reduce exposure to glucocorticoids (GCs) in this condition. The PBAC considered the key clinical data from the ADVOCATE trial suggested the magnitude of benefit that avacopan + standard of care (SOC) may provide in induction therapy compared to prednisolone + SOC was limited to a potential reduction in GC use with no significant benefit in remission at 26 weeks. In addition, the Committee considered the clinical evidence provided was inadequate to assess remission at 52 weeks and did not support comparative assessment of use as maintenance therapy. The PBAC considered the economic model was unreliable due to the uncertainties underpinning clinical data. Additional optimistic assumptions and inputs meant the PBAC considered the resulting incremental cost effectiveness ratio (ICER) was likely underestimated and highly uncertain.

7.2 The PBAC considered the primary reason for this outcome was due to the comparative clinical evidence provided.

7.3 The PBAC noted the comments from a health care professional and organisations that described the benefits of using avacopan combined with rituximab or cyclophosphamide in terms of a reduction in GC adverse effects. The PBAC noted the

comments from the Australian Rheumatology Association (ARA) that much of the treatment related morbidity in induction therapy can be attributed to GCs. The PBAC agreed with the comments from the Australian and New Zealand Vasculitis Society (ANZVASC) that there was a clinical need for treatments that allow avoidance of high, cumulative GC use in this condition.

7.4 The PBAC noted both the sponsor hearing and ANZVASC commented that the rapid weaning off GC between weeks 20–21 in the ADVOCATE trial was not reflective of clinical practice, which PBAC considered may have led to an overestimation of treatment benefit with avacopan monotherapy compared to no therapy at 52 weeks. The PBAC also confirmed during the sponsor hearing that rituximab is widely used in the maintenance setting, if tolerated. The PBAC noted the ADVOCATE trial was not designed to study the most clinically relevant comparison in the maintenance setting of avacopan + SOC with rituximab + SOC. The PBAC also noted the consumer comments did not support avacopan monotherapy in the maintenance setting, although this option was suggested in the submission and allowed with the proposed PBS restriction.

7.5 With respect to the proposed restriction the PBAC advised:

- Avacopan would be suitable for re-induction therapy based on its mechanism of action (see paragraph 3.2).
- A listing for maintenance therapy was not adequately supported by the clinical evidence provided in the submission (see paragraph 6.37).
- The use of avacopan as monotherapy was not consistent with the TGA approval nor the evidence provided in the submission and hence the restriction should specify 'Patient must be undergoing concomitant therapy with at least another drug therapy as part of a regimen specified in this drug's approved Product Information including either: i) cyclophosphamide; ii) rituximab.'

7.6 The PBAC considered that the nominated comparator GCs was appropriate in the induction phase. The PBAC agreed with the ESC that the comparison with 'no treatment' in the maintenance setting was not consistent with clinical practice nor international guidelines (EULAR 2022), and hence was not appropriate. The PBAC suggested a resubmission requesting treatment in the maintenance of remission should consider comparison of avacopan with rituximab versus rituximab, noting that rituximab maintenance is recommended in the EULAR 2022 guidelines and used in current clinical practice. As raised by ANZVASC, it was noted that the safety and clinical effects of avacopan beyond 52 weeks were not addressed in the trial and therefore its role in maintenance therapy remains unclear. The PBAC also noted monotherapy avacopan was not supported by the TGA indication nor international treatment guidelines.

7.7 The key trial evidence (ADVOCATE) was a head-to-head trial comparing avacopan + SOC to prednisone + SOC in patients with severe active GPA or MPA (N=331). All

patients received one of three SOC regimens including IV or oral cyclophosphamide followed by azathioprine or mycophenolate mofetil from Week 15 onwards or weekly IV rituximab for the first 4 weeks followed by no treatment. The PBAC agreed with the ESC and the Pre-Sub-Committee response (PSCR) that the ADVOCATE trial included both induction and maintenance therapy up to 52 weeks. However, the PBAC noted the maintenance phase included a comparison with patients who were on a background of either azathioprine or mycophenolate mofetil (following cyclophosphamide) or no further treatment (following rituximab induction). The PBAC agreed with the ESC that the latter was not consistent with current clinical practice, nor international guidelines (EULAR 2022) and, therefore, had no relevance to the current submission.

7.8 The PBAC acknowledged the concerns raised by the ESC regarding differences across treatment arms in GC use during the pre-screening period (see paragraph 6.14) but considered the impact of these differences (in the context of the total GC use during the 52 week treatment period) may be minimal.

7.9 The primary efficacy outcomes of the ADVOCATE trial were disease remission (Week 26) and sustained remission (Week 52). The PBAC agreed with the ESC that the week 26 and 52 results were relevant to induction therapy and maintenance therapy respectively. At Week 26, avacopan + SOC was non-inferior to prednisone + SOC in achieving disease remission, however superiority was not demonstrated. Despite this, the PBAC noted that the total study and non-study supplied GC dosage required during the induction period was lower in avacopan + SOC group (1373.7 mg) relative to prednisone + SOC group (3364.0 mg). The PBAC considered that the evidence provided indicated avacopan may provide a benefit in terms of a strategy to reduce exposure to GCs over the induction period.

7.10 In contrast to the disease remission results at Week 26, the submission reported that avacopan + SOC was superior to prednisone + SOC in achieving sustained remission at Week 52 (12.5% estimate of common difference, 95% CI: 2.6% to 22.3%; p=0.0066 for superiority). However, the PBAC noted that neither arm had study allocated prednisolone beyond 20 weeks and, as outlined in paragraph 7.7, considered a comparison with no further treatment (following rituximab induction) was not consistent with current practice. The PBAC noted that the subgroup analysis for those receiving azathioprine or mycophenolate mofetil as maintenance (following cyclophosphamide) indicated there may be no benefit in sustained remission at 52 weeks with the addition of avacopan (see paragraph 6.26). The PBAC agreed with the ESC that the modest 12.5% difference in the proportion of patients achieving sustained remission between the two treatment arms was likely driven by those who were not on any maintenance therapy after rituximab. The PBAC noted the pre-PBAC response and sponsor hearing argued that the 12.5% difference was not modest and would be clinically meaningful. However, PBAC considered in the context of no benefit in remission at 26 weeks, the value of this result at 52 weeks was difficult to ascertain, given a comparator arm that is not reflective of clinical practice. Overall, the PBAC

considered the clinical evidence provided did not adequately support use as maintenance therapy.

7.11 The PBAC noted the improvement in eGFR rates at both Week 26 and Week 52 evident for the population with renal disease included for this secondary outcome (see Table 7). However, the PBAC noted that other parameters of renal disease such as urinary albumin:creatinine ratio (UCAR) at Week 52 and urinary MCP-1 to creatinine ratio at Week 52 did not show any significant difference in patients with renal disease (see Table 7). The PBAC agreed with the ESC that the improvement in eGFR appeared to be driven by the eGFR < 30 ml/min/1.73m^2 subgroup (see Table 8) and that it was not clear how much of the benefit was attributable to the group which compared avacopan to no maintenance therapy (see paragraph 6.30).

7.12 Overall, the PBAC considered the claim of superior comparative effectiveness for avacopan + SOC compared to prednisolone + SOC was highly uncertain for induction therapy.

7.13 The PBAC noted the avacopan + SOC group had a higher incidence of moderate TEAE (49.4%) compared to the prednisone + SOC group (41.5%). In addition, patients in the avacopan + SOC group experienced higher incidences of several serious adverse events (see paragraph 6.32). However, the PBAC noted there were fewer treatment emergent infections and also a statistically significant reduction in potentially GC-related AE in favour of avacopan + SOC compared to prednisone + SOC (treatment difference of -14.2 percentage points; 95% CI -23.7 to -3.8; p<0.05) (see paragraph 6.33). Overall, the PBAC considered the claim of superior comparative safety was reasonable for the induction phase, noting there was no safety evidence on the cumulative risk of reinduction or long-term safety data for maintenance treatment.

7.14 The PBAC considered the economic model was unreliable due to the uncertainties in the clinical data from the ADVOCATE trial (see paragraph 7.12). The PBAC noted the economic model assumed that patients would be treated with avacopan over 24 months (6 months of induction, followed by 18 months of maintenance). The PBAC considered the extrapolation of data from the 52 week ADVOCATE trial to impacts on renal disease progression and mortality over 30 years increased the uncertainty in the cost-effectiveness estimates. The PBAC considered the benefits modelled for induction should be limited to the differences in the adverse event profiles.

7.15 The PBAC noted DUSC advice that the estimated use of avacopan was aligned with the previous use of rituximab for the same indications between 2016-2022 and that avacopan was unlikely to increase the patient population. The PBAC agreed with the DUSC that the remaining uncertainty with respect to the eligible population could be reduced by removing Population 3 from the financial model. In addition, the PBAC agreed with the DUSC that grandfathered patients could be removed from the financial model as these patients would have been counted from the prevalent pool. The PBAC noted that the duration of treatment included assumptions regarding maintenance therapy and reiterated that the clinical evidence provided did not

adequately support such use.

7.16 The PBAC considered a resubmission for avacopan should be based on the benefits of reducing GC when used as induction therapy. Additional clinical evidence would be required to support broader benefits, including efficacy benefits, when used as induction therapy or to support use as maintenance therapy. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.