# 7.03 AVACOPAN, Capsule 10mg, Tavneos®, Seqirus (Australia) Pty Ltd

## 1 Purpose of submission

1.1 The standard re-entry resubmission requested Section 85, Authority Required (Streamlined) 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.

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

| Component | Description |
|---|---|
| **Population** | Adult patients with newly diagnosed or relapsed ANCA-associated vasculitis severe active GPA and severe active MPA defined as at least one major or three non-major items or at least two renal items of haematuria and proteinuria on the BVAS |
| **Intervention** | Avacopan in combination with rituximab (induction)/rituximab (maintenance) or cyclophosphamide (induction)/azathioprine (maintenance) |
| **Comparator** | GCs which is used as SOC concomitantly with rituximab (induction)/rituximab (maintenance) or cyclophosphamide (induction)/azathioprine (maintenance) |
| **Outcomes** | **Primary**<br>• Induced and sustained disease remission<br>**Secondary**<br>• GC-induced toxicity<br>• Rapidity of response in the avacopan group compared to the prednisone group<br>• Safety in the avacopan group compared to the prednisone group<br>• Health-related quality of life changes<br>• Changes in parameters of renal disease<br>• Changes in cumulative organ damage |
| **Clinical claim** | In AAV, avacopan is superior compared to GC SOC in terms of both efficacy and safety when administered for a treatment duration not exceeding 52 weeks per severe disease flare. |

Source: Table 1.2, Avacopan resubmission
Abbreviations: AAV ANCA-associated vasculitis; BVAS Birmingham Vasculitis Activity Score; GC, glucocorticoids; GPA granulomatosis with polyangiitis; MPA microscopic polyangiitis; SOC, Standard of care;
Blue shading indicates information previously seen by the PBAC. The resubmission maintained a claim of superiority over glucocorticoid SOC in terms of both safety and efficacy but added the stipulation that this was only when avacopan was administered for a treatment duration not exceeding 52 weeks per severe disease flare.

## 2 Background

### *Registration status*

2.1 Avacopan received Therapeutic Goods Administration (TGA) registration 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 (GPA and MPA).

## *Previous PBAC consideration*

2.2 This is the second PBAC consideration of avacopan for the treatment of severe active GPA and MPA. The previous submission for avacopan was considered by the PBAC in July 2023 and was not recommended. The main PBAC concerns and how they were addressed in the resubmission are summarised in Table 2.

**Table 2: Summary of key matters of concern**

| Component | Matters of concern | How the resubmission addresses it |
|---|---|---|
| New evidence provided | 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 (para 7.16, avacopan, PSD, July 2023 PBAC meeting). | Partially addressed.<br>Additional evidence provided:<br>• Post-hoc analysis of time to 40% reduction in urinary albumin creatinine ratio (UACR)<br>• Post-hoc analysis of patient-reported health-related quality of life outcomes (already considered at the July 2023 meeting)<br>• A systematic review of GC-specific adverse events in patients with AAV<br>• Supplementary real-world evidence from the avacopan Expanded Access Program<br>• Feasibility assessment of three randomised controlled trials (MAINRITSAN, MAINRITSAN 2 and RITZAREM) which considered the use of rituximab for maintenance, but no indirect treatment comparison (ITC) undertaken.<br>The new information provided in the resubmission does not adequately address previous concerns raised regarding no comparative benefit for remission at 26 weeks and no relevant comparative assessment of sustained remission for maintenance therapy from 26–52 weeks. |
| Restriction | The PBAC suggested that the restriction specifies that the '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.' (para 7.5, avacopan, PSD, July 2023 PBAC meeting). The PBAC noted the use of avacopan as monotherapy was not supported by its TGA indication or treatment guidelines (para 7.6, avacopan, PSD, July 2023 PBAC meeting).<br><br>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 (para 6.38, avacopan, PSD, July 2023 PBAC meeting). | Addressed.<br>Restriction amended with "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; or ii) rituximab".<br><br>Not adequately addressed.<br>The resubmission requested a single restriction for the use of avacopan in either induction, maintenance, or reinduction with the additional stipulation of a maximum treatment duration of 12 months per disease flare. The ESC advised the uncertainties associated with other benefits |

| Component | Matters of concern | How the resubmission addresses it |
|---|---|---|
| | | outside of steroid sparing effect and use in the maintenance phase remain. |
| Comparator (maintenance setting) | 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 para 7.6, avacopan, PSD, July 2023 PBAC meeting) | Addressed in the restriction and economic model. The resubmission acknowledged that in clinical practice avacopan is unlikely to be used as monotherapy. Rituximab as a comparator has been added to the economic model. |
| Clinical claim | 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 (para 6.38, avacopan, PSD, July 2023 PBAC meeting). | Not adequately addressed.<br>The resubmission revised the clinical claim to describe avacopan as superior for effectiveness and safety compared to GC + SOC when administered for a duration of up to 52 weeks per severe disease flare. However, despite new information provided in the resubmission, previous concerns and limitations to robust supportive data remain. |
| Comparative effectiveness (maintenance setting) | The PBAC considered the clinical evidence provided was inadequate to assess remission at 52 weeks and did not support comparative assessment of use as maintenance therapy (para 7.1, avacopan, PSD, July 2023 PBAC meeting). | Partially addressed.<br>The resubmission redefined the maintenance phase to be 'maintenance of remission' representing months 6-12 from start of induction. Additional analyses from the ADVOCATE trial (as described above) were used to demonstrate improvements in eGFR, time to 40% UACR reduction, improvements in health-related quality of life outcomes at week 52 and EAP safety data for 30 patients (some with longer treatment). The resubmission considered an ITC between avacopan and rituximab maintenance treatment but did not undertake one citing limitations and transitivity issues. In the economic model, the resubmission applied an adjustment of the hazard ratio for relapse to account for the impact of adding rituximab to avacopan in maintenance. |
| Economic model | The PBAC considered the extrapolation of data from the 52-week ADVOCATE trial to impact 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 (para 7.14, avacopan, PSD, July 2023 PBAC meeting). The PBAC considered a resubmission 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 (para 7.16, avacopan, PSD, July 2023 PBAC meeting). | Partially addressed.<br>The resubmission stated the sponsor was unable to proceed with a PBS listing for avacopan based on benefits of reducing glucocorticoids alone. The following have been addressed in the revised economic evaluation:<br>• The time horizon has been reduced from 30 to 20 years.<br>• The maximum avacopan treatment duration per disease flare has been reduced from 24 to 12 months, with 1 reinduction.<br>• Treatment waning of avacopan has been reduced from 1 year to 6 months.<br>• Rituximab use has been modelled in the maintenance phase for both treatment arms.<br>• The HR for eGFR improvement and ESRD risk has been increased from 0.90 to 0.955. |

| Component | Matters of concern | How the resubmission addresses it |
|---|---|---|
| | | • The effective price of avacopan has been reduced by [redacted]% from $[redacted] to $[redacted] per capsule (AEMP reduced from $[redacted] to $[redacted]).<br>• The resultant average treatment cost per patient per course of treatment is a reduction of [redacted]% from $[redacted] to $[redacted]. |
| Financial estimates | 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.<br><br>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 (para 7.15, avacopan, PSD, July 2023 PBAC meeting). | New information. The resubmission provided new incidence figures from a new source (Queensland hospital admission data) which are substantially higher than the previous submission.<br><br>Partially addressed. The treatment duration in the financial estimates has been revised to 9.6 months to reflect new restriction of a maximum 12 months therapy. It remains uncertain if the clinical evidence adequately supports such use. |

Source: Compiled during the evaluation
Abbreviations: DUSC, Drug Utilisation Sub Committee; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; PBAC, Pharmaceutical Benefits Scheme; PSD, public summary document; SOC, standard of care; TGA, Therapeutic Goods Administration; UACR, urine albumin-creatinine ratio.

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

# 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|---|
| AVACOPAN | | | | | | |
| avacopan 10 mg capsule, 180 | $8,485.33 published price $[redacted] effective price | NEW 1 MP | 1 | 180 | 5 | Tavneos |
| | | | | | | |
| | | | | | | |
| **Restriction Summary [new 1] / Treatment of Concept: [new 1.1] Authority Required (STREAMLINED)** | | | | | | |
| | **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
| | **Prescriber type: Prescriber type:** ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives | | | | | |
| | **Restriction type:** ☒Authority Required (STREAMLINED) | | | | | |
| | **Episodicity:** [blank] | | | | | |
| | **Severity:** [blank] | | | | | |
| | **Condition:** Anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis | | | | | |
| | **Indication:** Anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis | | | | | |
| | | | | | | |
| | **Treatment phase:** Induction ~~or~~, reinduction or maintenance of remission | | | | | |

| | |
|---|---|
| | |
| | **Clinical criteria:** |
| | The condition must be severe granulomatosis with polyangiitis; or |
| | The condition must be severe microscopic polyangiitis |
| | **AND** |
| | **Clinical criteria:** |
| | The condition must be active at the time of the first prescription for this drug |
| | |
| | **Treatment criteria:** |
| | *Patient must be at risk of end-organ damage or mortality* |
| | 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 |
| | **AND** |
| | **Treatment criteria:** |
| | Patient must be undergoing initial treatment with this drug; or |
| | Patient must be undergoing continuing treatment with this drug, with an improvement in the condition; or |
| | Patient must be undergoing a resumption of treatment with this drug, with a break in therapy having occurred for any reason other than a lack of drug effectiveness; or |
| | Patient must be undergoing continuing treatment, where current treatment is with non-PBS-subsidised supply, but the length of treatment duration has been reasonably insufficient for complete resolution of active disease symptoms |
| | **AND** |
| | Patient must not receive more than 12 months of treatment with this drug |

3.2 The resubmission proposed a special pricing arrangement (SPA). The proposed effective EMP and DPMQ of avacopan were $ and $, respectively. The requested effective EMP is % lower than the price proposed in the previous submission (July 2023 submission EMP $). The pre-PBAC response offered a further % price reduction from an EMP of $3 to $ and noted this was a % reduction from the July 2023 submission.

3.3 The proposed population in Table 1 is defined as severe active GPA or MPA. The 2022 update to the EULAR recommendations suggested that 'severe/non-severe' terms may be variably defined and misleading in clinical practice. The guideline maintained the use of 'active' GPA or MPA. The proposed restriction lacks clear definitions for both severe and active disease. Without clear definitions, this may lead to use outside of the proposed restriction. According to EULAR, active disease refers to the presence of typical signs, symptoms or other features (such as glomerulonephritis or pulmonary nodules) of active AAV. The Pre-Sub-Committee Response (PSCR) suggested the inclusion of a clinical criterion 'Patient must be at risk of end-organ damage or mortality' to align the eligible patient population with the intended definition of disease severity. The ESC considered the addition of this criterion appropriate and noted it was consistent with the previous rituximab listing for this indication. The PBAC noted EULAR guidelines use the terminology 'organ-threatening or life threatening' disease.

3.4 The restriction for induction treatment does not specify a limit on the number of times avacopan may be used for reinduction following relapse. Given the limited longer-term safety and efficacy data for avacopan, it is unclear if unlimited reinductions is reasonable. However, DUSC considered the availability of avacopan beyond two reinductions would be clinically important and would have minimal impact on the financial estimates as few patients would likely require more than two reinductions (para 6.80, avacopan Public Summary Document (PSD), July 2023 PBAC meeting).

3.5 The inclusion of maintenance treatment was not previously supported by the PBAC who at that time considered the evidence provided was inadequate to assess remission at 52 weeks and did not support comparative assessment of use as maintenance therapy (para 7.1, avacopan PSD, July 2023 PBAC meeting). The proposed restriction in the resubmission has limited duration of treatment with avacopan to 12 months, however, it remains unclear whether the resubmission's interpretation of the additive benefit of avacopan to rituximab is acceptable given no direct or indirect evidence is available for this assessment.

3.6 Interpretation of the wording for the 12-month treatment limit is unclear in the requested listing. The requested listing does not specify if this is per disease flare. It is uncertain whether the proposed 12-month limit on treatment duration is expected to commence at the start of any of the three listed treatment phases, whether it is expected that treatment is allowed for any of these phases within a defined 12-month period or whether this is a total 12 month limit per patient. The PSCR clarified that the intent is to limit the duration of avacopan therapy to 12 months per treatment cycle, inclusive of induction or reinduction. The PSCR proposed the addition of 'per treatment cycle' to the wording of the treatment criterion. The ESC considered that restricting use to allow for 12 months of use after induction/re-induction may be reasonable, accepting there remains uncertainties associated with other benefits outside of steroid sparing effect and use in maintenance phase.

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

# 4 Population and disease

4.1 ANCA-associated vasculitis (AAV) is a collection of relatively rare autoimmune diseases characterised by inflammatory cell infiltration causing necrosis of blood vessels. AAV is classified based on antibody status or clinical phenotype: status of PR3-ANCA+ is linked to GPA whereas MPO-ANCA+ is linked to MPA. AAV can involve many organs, with the kidneys, respiratory tract, nose/sinuses, eyes, skin, and nervous system 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. AAV can present at any age, with diagnosis commonly occurring between the age of 55 to 74.

4.2 The lived experience of AAV patients is important to consider in disease management due to the systematic nature of the disease which can affect multiple organs. The resubmission included a report presenting the perspectives of three AAV patients. The three key themes that emerged from these patients were:

- Quality of life – experiencing life with reduced disease and treatment burden with improved disease management;
- Clinical improvement – the ability to feel well for longer periods of time; and
- Hope for the future – representing potential, hope and redefining reality of living with a life-limiting disease.

4.3 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 (GCs) or rituximab plus GCs are considered SOC. For maintenance treatment, tapered GCs in combination with either rituximab or azathioprine are primarily 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. 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 GCs. The PBAC noted that the EULAR guidelines recommend that therapy to maintain remission be continued for 24–48 months following induction of remission of new-onset disease. Longer duration of therapy should be considered in relapsing patients or those with an increased risk of relapse, but should be balanced against patient preferences and risks of continuing immunosuppression.

4.4 Avacopan is proposed to be used concomitantly with other immunosuppressive therapy (rituximab, cyclophosphamide or azathioprine), in a similar manner to GCs. The PBAC noted that the EULAR guidelines recommend that 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.[1] The PBAC noted that the Kidney Disease Improving Global Outcomes (KDIGO) 2024 clinical practice guidelines stated that avacopan may be used as an alternative to GCs. In addition, the KDIGO guidelines stated that patients with an increased risk of GC toxicity are likely to receive the most benefit from avacopan and that patients with lower GFR may benefit from greater glomerular filtration rate recovery.[2] Neither of these treatment guidelines include avacopan in the maintenance setting.

[1] Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, et al. EULAR Recommendations for the Management of ANCA-Associated Vasculitis: 2022 Update. Ann Rheum Dis. 2023; 0: 1-18

[2] Floege J, Jayne DRW, Sanders JF, Tesar V, Rovin BH. KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis. Kidney International. 2024;105 (3):S71–116.

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 resubmission nominated GCs as the comparator. This was unchanged from the previous submission. That 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 GCs. The PBAC previously considered that the nominated comparator GCs was appropriate in the induction phase (para 7.6, avacopan, PSD, July 2023 PBAC meeting).

5.2 To maintain remission (up to 12 months from start of induction), avacopan would be used concomitantly with a maintenance regimen (typically rituximab or azathioprine, and optionally GCs at reduced doses). The 2022 EULAR guidelines recommend the use of rituximab monotherapy for the maintenance phase of AAV treatment. In July 2023, the PBAC considered that a comparison with 'no treatment' in the maintenance setting for those who had received rituximab induction was not consistent with clinical practice or clinical guidelines. Consequently, the PBAC recommended that a resubmission requesting treatment in the maintenance of remission should consider comparison of avacopan with rituximab versus rituximab (para 7.6, avacopan, PSD, July 2023 PBAC meeting). The resubmission suggested the clinically relevant comparators for avacopan in the maintenance phase are rituximab (plus tapering GCs) for those on GCs and rituximab at induction and azathioprine (plus tapering GCs) for those on GCs and cyclophosphamide at induction.

*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 mechanism of action for avacopan, how this is differed from currently available treatments, and its anticipated clinical place in practice. The clinician suggested that the majority of severe AAV patients being treated with rituximab or cyclophosphamide in Australian clinical practice have impaired renal function and are likely to derive the same outcomes of early renal improvement as observed in the ADVOCATE trial, especially for those patients whose EGFR is at the lower end of the range. The clinician noted the importance of quality of life improvements from reduced GC use in this population

and presented a clinical case study. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease. The PBAC confirmed that data is not available on reinduction. However, the clinician proposed that avacopan would likely be suitable for reinduction therapy based on its mechanism of action. The PBAC also confirmed that the role of avacopan in maintenance therapy remains unclear as there are no further trial data on its safety and clinical effects beyond 52 weeks.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (17) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals who have used this medicine for their own health condition described a range of benefits of treatment with avacopan including the ability to halt other treatments (primarily GCs) that had been negatively impacting blood sugar levels, bone density and wound healing. Individuals who would like to access the medicine to treat their own health condition described the lack of efficacy of other treatment options in controlling GPA or MPA symptoms and expressed a hope that avacopan would address these treatment gaps. Input from a parent, partner or another person directly caring for an individual with this condition described the side effects associated with GCs and noted the reduced side effects reported during avacopan treatment in comparison. The comments from the Australian & New Zealand Vasculitis Society concord with the concerns raised by individuals regarding the side effect profile of GCs.

6.3 The PBAC noted the advice received from the Australian Rheumatology Association and the Australasian Society of Clinical Immunology and Allergy clarifying the likely use of avacopan in clinical practice. The PBAC specifically noted the advice from the Australian Rheumatology Association that the use of avacopan may result in: longer time to relapse compared with standard of care; improvement in kidney function and delayed time to dialysis; and improved quality of life and reduced toxicity compared with current standard of care.

## *Clinical trials*

6.4 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. 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 trial presented in the resubmission was the same as in the previous submission. The duration of follow-up remains the same as in the previous submission. There are 6 new abstracts/publications included in the resubmission that are post hoc or

subgroup analyses of the ADVOCATE trial data. Some of these analyses are newly presented in the resubmission.

6.5 As there was no direct evidence comparing avacopan and rituximab in the maintenance setting, the resubmission included three randomised controlled trials (MAINRITSAN, MAINRITSAN 2 and RITZAREM) which considered the use of rituximab for maintenance for consideration of an ITC. No ITC was undertaken in the resubmission (see paragraph 6.33).

6.6 Details of the trials presented in the resubmission are provided in Table 3.

**Table 3: Trials and associated reports presented in the resubmission**

| 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 |
| | Cortazar, F. B., Jayne, D. R., Bruchfeld, A., Bekker, P. 2022. Renal Recovery for Patients With Baseline eGFR <=20 in Avacopan ADVOCATE Trial [abstract]. | *J Am Soc Nephrol, 33:501.* |
| | Jayne D., Merkel P., Cortazar F., et al. 2022. Recovery of Renal Function Among ANCA-Associated Vasculitis Patients with Baseline eGFR ≤20 in the Avacopan ADVOCATE Trial [abstract]. | *Arthritis Rheumatol. 74(Suppl 9):1056-1057.* |
| | Patel N., Jayne D., Merkel P., et al. 2022. ANCA-Associated Vasculitis Treated with Avacopan versus a Standard Prednisone Taper: Glucocorticoid Toxicity Index Scores by Domain [abstract]. | *Arthritis Rheumatol; 74(Suppl 9):2141-2142.* |
| | Patel N., Jayne D., Merkel P., et al. 2023. Glucocorticoid Toxicity Index scores by domain in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with avacopan versus standard prednisone taper: post-hoc analysis of data from the ADVOCATE trial. | *Lancet Rheumatol, 5(3):e130-e138.* |
| | Geetha D., Cortazar F., Karras A., et al. 2023. #3236 Change in albuminuria in patients with ANCA-associated vasculitis treated with avacopan. | *Nephrol Dial Transplant, 38(Suppl 1): i296-i298.* |
| | Strand V., Jayne D., Horomanski A., et al. 2023. The impact of treatment with avacopan on health-related quality of life in anti-neutrophil cytoplasmic antibody-associated vasculitis: a post-hoc analysis of data from the ADVOCATE trial. | *Lancet Rheumatol, 5(8):e451-e460.* |
| MAINRITSAN NCT00748644 | Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. | *N Engl J Med. 2014;371(19):1771-1780.* |
| MAINRITSAN 2 NCT01731561 | Charles P, Terrier B, Perrodeau É for the French Vasculitis Study Group, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2) | *Annals of the Rheumatic Diseases 2018;77:1143-1149.* |
| RITAZAREM NCT01697267 | Smith RM, Jones RB, Specks U RITAZAREM co-investigators, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial | *Annals of the Rheumatic Diseases 2023;82:937-944.* |

Source: Table 2.6, p53 of the resubmission, Table 2.7, pp53-54 of the resubmission
Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.
Blue Shading indicates information previously seen by the PBAC
Note: The three rituximab trials, MAINRITSAN, MAINRITSAN 2, and RITAZAREM are not discussed in detail in the main body of the resubmission but are more comprehensively described in Attachment 18 of the resubmission.

6.7 The key features of the randomised trials are summarised in Table 4.

**Table 4: Key features of the trials 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<br>52-week treatment period | Low/some concerns | Severe active GPA or MPA | Primary: Disease remission (Week 26) and sustained remission (Week 52)<br><br>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). |
| **Rituximab maintenance trials** | | | | | |
| MAINRITSAN | 115 | Rituximab versus azathioprine<br><br>R, OL, AC<br>28-month treatment period | Low/some concerns | GPA, MPA or renal-limited AAV | Primary: Percentage of patients with major relapse[a] (Month 28)<br><br>Secondary: Rates of minor relapse[b] (Month 28), rates of AEs and SAEs (Month 28), and mortality (Month 28). |
| MAINRITSAN 2 | 162 | Individually tailored versus fixed-schedule rituximab<br><br>R, OL, AC, MC<br>28-month treatment period | Low | Patients in remission with GPA or MPA | Primary: Number of relapses (Month 28)<br><br>Secondary: Number of major relapses[a] (Month 28); number of minor relapses[b] (Month 28); association of ANCA evolution and CD19+ B cell counts with relapses (Month 28); GC duration and cumulated dose (Month 28); Vasculitis Damage Index (VDI) evaluated damage severity and number for each group (Month 28); AEs (Month 28); and mortality (Month 28). |
| RITAZAREM | 188 | Rituximab versus azathioprine<br><br>R, OL, AC, MC<br>24-month treatment period | Some concerns | Relapsing GPA or MPA and PR3+ or MPO+ | Primary: Time from randomisation to disease relapse<br><br>Secondary: Proportion who maintained remission at the end of the maintenance phase (Month 24), or end of the follow-up phase (Month 36); time to major relapse[c]; cumulative accrual of damage measured by the Combined Disease Assessment instrument (Month 24 and Month 36); cumulative GC exposure (Month 36); health-related quality of life measures using the SF-36 (Month 24 and Month 36); rates of SAEs (Month, hypogammaglobulinaemia, defined as plasma IgG<5 g/L and infections (Ongoing). |

Source: Table 2.7, pp53-54 of the resubmission, and Attachment 8.

Abbreviations: AC, active-controlled; DB, double-blind; DD, double-dummy; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; HRQoL, health-related quality-of-life; MC, multicentre; MPA, microscopic polyangiitis; OL, open-label; R, randomised; SOC, standard of care.

[a] In MAINRITSAN and MAINRITSAN 2, major relapses were defined as the reappearance or worsening of disease with a BVAS >0 and involvement of at least one major organ or a life-threatening manifestation.

[b] In MAINRITSAN and MAINRITSAN 2, minor relapses were defined as the reappearance or worsening of disease with a BVAS >0, not corresponding to a major relapse but requiring mild treatment intensification.

[c] Major relapses were defined in RITAZAREM as the development of a new or recurrent major disease activity item using the BVAS

Blue Shading indicates information previously seen by the PBAC

6.8 The resubmission did not update their risk of bias claim for the ADVOCATE trial. In July 2023, an overall low/some concerns rating for the risk of bias from the ADVOCATE trial was considered appropriate given there were some concerns for risk of attrition bias (para 6.11, avacopan PSD, July 2023 PBAC meeting).

6.9 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.

6.10 The resubmission 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.

6.11 For the primary efficacy outcomes, patients who discontinued from the study before the Week 26 disease remission endpoint or Week 52 sustained remission endpoint, or patients with missing data were conservatively imputed as 'not in remission'. For the secondary efficacy outcomes, the handling of patients who discontinued from the study was not reported, and there was either no reporting or imputation of missing data.

6.12 During the 52-week treatment period in the ADVOCATE trial, the avacopan + SOC group had a higher mean cumulative dose of non-study supplied GCs in prednisone-equivalent units (1675.5 mg) across the entire treatment period compared to the prednisone + SOC group (1457.6 mg). 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. However, the total study and non-study supplied GC dosage required during the first 26 weeks was lower in avacopan + SOC group (1373.7 mg) relative to prednisone + SOC group (3364.0 mg).

## *Comparative effectiveness*

6.13 The ADVOCATE trial remains the primary source of clinical effectiveness information which has been seen by the PBAC before. The resubmission newly presents subgroup analyses from ADVOCATE. The resubmission also newly presents randomised trials for rituximab in the maintenance setting. The ESC noted that there remains no direct or indirect evidence to assess the efficacy of avacopan in combination with rituximab versus rituximab in the maintenance setting.

6.14 Table 5 presents the results of the primary efficacy outcomes, disease remission and sustained remission, from the ADVOCATE trial.

**Table 5: 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) [b] | 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) [b] | 12.5 (2.6, 22.3) | <0.0001 | 0.0066 |

Source: Table 2.26, p84 of the resubmission, Table 2.27, p84 of the resubmission, Table 13, p88 of the ADVOCATE CSR and Table 15, p90 of the ADVOCATE CSR.

Abbreviations: CI, confidence interval; ITT, intention to treat; SOC, standard of care.

[a] Summary score estimate of the common difference in remission rates by using inverse-variance stratum weights.

[b] Calculated during the evaluation.

Blue Shading indicates data previously seen by the PBAC

6.15 At Week 26, avacopan + SOC was non-inferior to prednisone + SOC in achieving disease remission, and superiority was not demonstrated. 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).

6.16 The total study and non-study supplied GC dosage required during the initial 6 months was lower in avacopan + SOC group (1373.7 mg) relative to prednisone + SOC group (3364.0 mg), and as a result, there may be advantages in other patient-relevant secondary efficacy outcomes such as GC-induced toxicity. The PBAC had previously noted the lower dose of GCs required during the induction period in the avacopan + SOC group and considered the evidence provided indicated that avacopan may provide a benefit in terms of a strategy to reduce exposure to GCs over the induction period (para 7.9, avacopan, PSD, July 2023 PBAC Meeting).

6.17 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) | 10.8 (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) [a] | 11.2 ( -0.3, 22.7) |
| | Without renal disease | 18/32 (56.3) | 14/30 (46.7) [a] | 9.6 ( -15.2, 34.4) |

Source: Table 2.26, p84 of the resubmission, Table 2.39, p106 of the resubmission, Table 14.2.2.9, pp340-341 of Attachment 9.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic autoantibody; CI, confidence interval; GPA, granulomatosis with polyangiitis; ITT, intention to treat; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; SOC, standard of care.
[a] Corrected during the evaluation.
Blue Shading indicates data previously seen by the PBAC

6.18 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 followed by azathioprine 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 subsidy under the proposed restriction, these subgroups show weaker treatment effect in achieving sustained remission from avacopan + SOC over the comparator. The ESC had previously 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 and 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 was likely driven by those who were not on any maintenance therapy after rituximab (para 6.26, avacopan, PSD, July 2023 PBAC Meeting).

6.19 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.

**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 m$^2$, 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 m$^2$, 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, pp83-105 of the resubmission.

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, intention 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.

Blue Shading indicates data previously seen by the PBAC

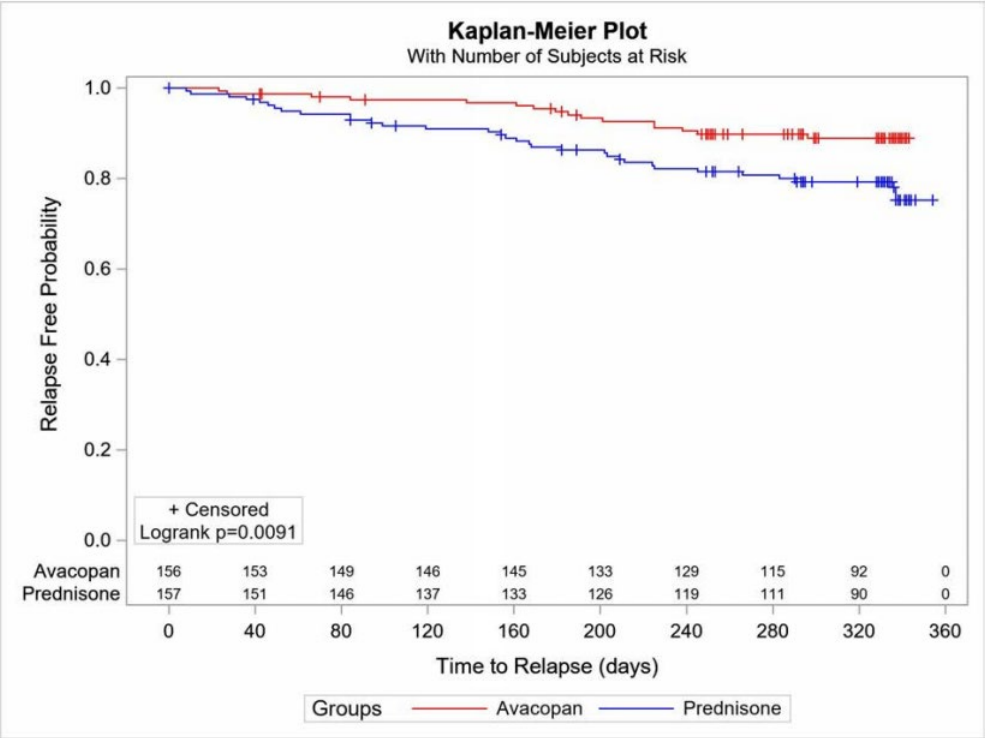
6.20 Avacopan + SOC showed statistically significant improvement in several patient-relevant secondary outcomes, including reduced GC-induced toxicity on both the GTI-CWS and GTI-AIS, improved HRQoL on the EQ-5D-5L visual analogue scale (VAS) and Index score, and improved renal disease parameters. Furthermore, the rate of relapse at any time during the study after complete remission was reduced significantly by

54% (hazard ratio [HR] 0.46, 95% CI: 0.25, 0.84; p=0.0091) in the avacopan group + SOC (10.1%) compared to the prednisone + SOC group (21.0%).

6.21 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.

6.22 The resubmission also highlighted the results of an exploratory analysis presented in the previous submission demonstrating a divergence in the Kaplan-Meier curve (Figure 1) at the time to relapse for the ADVOCATE treatment arms after 40 days. The resubmission stated this demonstrated the benefits of avacopan over background induction therapy. This exploratory analysis captured time to relapse from the first time point when BVAS = 0 was achieved. A large number of patients (up to 90%) were censored from the analysis and the reasons for this was not provided.

**Figure 1: Kaplan-Meier plot of time to relapse for ADVOCATE**




Source: Figure 2-4, p86 of the resubmission
Note: Data previously seen by the PBAC

6.23 Table 8 presents the results of a post hoc subgroup analysis for the change in estimated glomerular filtration rate (eGFR) from baseline after 26 weeks and 52 weeks. This was presented in the July 2023 submission's PSCR and has been considered by the PBAC.

**Table 8: Change in eGFR from baseline by subgroup**

| eGFR subgroup (mL/min/1.73m$^2$) | Avacopan + SOC | Prednisone + SOC | Mean Difference | p-value |
|---|---|---|---|---|
| **Week 26** | | | | |
| **Overall** | 5.8 | 2.9 | 2.9 | 0.046 |
| **<30** | 10.5 | 6.4 | 4.1 | 0.0361 |
| **31-59** | 7.3 | 5.4 | 1.9 | 0.3535 |
| **>59** | -2.6 | -6.0 | 3.4 | 0.3640 |
| **Week 52** | | | | |
| **Overall** | 7.3 | 4.1 | 3.2 | 0.029 |
| **<30** | 13.7 | 8.2 | 5.6 | 0.0050 |
| **31-59** | 10.5 | 7.8 | 2.7 | 0.2115 |
| **>59** | -5.9 | -7.5 | 1.6 | 0.6721 |

Source: Table 2-32, p.90 of the resubmission
Abbreviations: eGFR, estimated glomerular filtration rate; SOC, standard of care.
Blue Shading indicates data previously seen by the PBAC

6.24 In July 2023, the PBAC noted the improvement in eGFR rates at both Week 26 and Week 52 evident for the population with renal disease but agreed with the ESC that the improvement in eGFR appeared to be driven by the eGFR <30 mL/min/1.73m$^2$ subgroup and that it was not clear how much of the benefit was attributable to the group which compared avacopan to no maintenance therapy (para 7.11, avacopan, PSD, July 2023 PBAC Meeting). The pre-PBAC response for the resubmission argued that the ADVOCATE study demonstrated a statistically significant and clinically meaningful improvement in renal function as measured by eGFR at 52 weeks. The pre-PBAC response stated that this is acknowledged in the EULAR and KDIGO guidelines which recommend avacopan specifically for patients at risk of steroid adverse effects and complications or patients with active glomerulonephritis and rapidly deteriorating kidney function, amongst other patient populations.[3,4]

6.25 At the July 2023 meeting, the PBAC considered the key clinical data from the ADVOCATE trial suggested the magnitude of benefit that avacopan + 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. The Committee also considered the clinical evidence provided was inadequate to assess remission at 52 weeks and did not support comparative assessment of use as maintenance therapy (para 7.1, avacopan, PSD, July 2023 PBAC Meeting).

6.26 In July 2023, 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,

[3] Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, et al. EULAR Recommendations for the Management of ANCA-Associated Vasculitis: 2022 Update. Ann Rheum Dis. 2023; 0: 1-18

[4] Floege J, Jayne DRW, Sanders JF, Tesar V, Rovin BH. KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis. Kidney International. 2024;105 (3):S71–116.

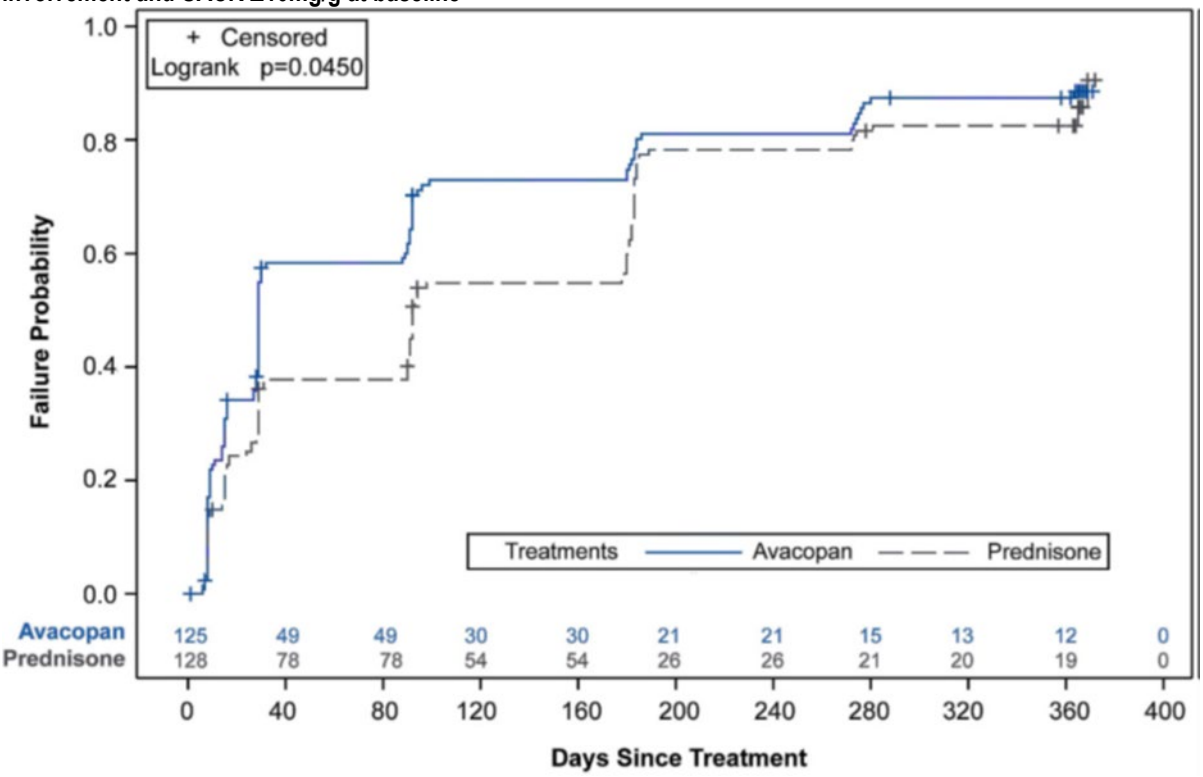
when used as induction therapy or to support use as maintenance therapy (para 7.1, avacopan, PSD, July 2023 PBAC Meeting).

6.27 New clinical effectiveness information presented in the resubmission included:

- Additional post-hoc and subgroup analyses from the ADVOCATE trial to demonstrate the broader benefits of avacopan.
  - Post-hoc analysis of time to 40% reduction in urinary albumin creatinine ratio (UACR) for participants with kidney involvement and baseline UACR ≥10mg/g.
  - Post-hoc analysis of patient-reported HRQoL outcomes. These data without the reference to minimum clinically important difference (MCID) and minimum important difference (MID) were presented in the previous submission and considered by the PBAC at the July 2023 meeting.
- A feasibility assessment of three randomised controlled trials (MAINRITSAN, MAINRITSAN 2 and RITZAREM) which considered the use of rituximab for maintenance as evidence to support why a comparison of avacopan vs rituximab for the maintenance phase was not feasible.

6.28 Figure 2 presents a Kaplan-Meier curve showing the time to achieve a 40% reduction in UACR for participants with kidney involvement and UACR ≥10mg/g at baseline in the avacopan and prednisone groups.

**Figure 2: Time to 40% UACR reduction in avacopan and SOC treatment groups for participants with kidney involvement and UACR ≥10mg/g at baseline**




Source: Figure 2.10, p.94 of the resubmission
Abbreviations: SOC, standard of care; UACR, urinary albumin to creatine ratio

6.29 The analysis demonstrated that the median time to achieve a 40% reduction in UACR was 29 days (95% CI, 29, 88) for the avacopan treatment group versus 92 days (95% CI, 91, 180) for the SOC group over the 52-week treatment period (log-rank p = 0.045).

6.30 After 52 weeks, there was no statistically significant difference in achieving a 40% reduction between participants in either treatment arms as the curves on the Kaplan-Meier converged at Day 200 (approximately 28 weeks).

6.31 The resubmission considered that the faster reduction in UACR in the avacopan group may have contributed to greater subsequent improvement in eGFR as a result of more rapid control of glomerular inflammation. This interpretation may be reasonable but would only apply to a subgroup of patients with kidney involvement and UACR ≥10mg/g. Translation of this outcome to long term benefits including improvement in eGFR is uncertain. It should also be noted that the baseline geometric mean UACR mg/g was reported to be higher in the avacopan + SOC group (433; range 20 to 6461) than the GC + SOC group (312; range 11 to 5367) and it unclear if the analysis adjusted for this baseline difference. The PSCR argued that the direct link between albuminuria and kidney damage is well-established and early and short-term albuminuria reduction has been shown to correlate with better clinical outcomes. The ESC noted the reduction in the median time to achieve a 40% reduction in UACR and considered that it may suggest a potential renal benefit in the subgroup of patients with kidney involvement and UACR ≥10mg/g. However, the ESC considered the selection of a 40% target appeared to be arbitrarily chosen to maximise the statistical difference and was not supported in the literature. Overall, the ESC advised that the broader implications of the 40% reduction in UACR were unclear. The pre-PBAC response stated that 30% is the target reduction UACR generally accepted in the literature[5] and acknowledged the target used in the post-hoc analysis was higher than that generally accepted. However, the pre-PBAC response argued that the speed of UACR improvement in the avacopan group versus SoC would remain if this threshold was set lower at 30% target reduction. The pre-PBAC response stated the speed of UACR decrease is relevant because it provides a potential mechanistic rationale for the clinically meaningful improvement in eGFR observed in the avacopan cohort at 52 weeks.

6.32 The resubmission also provided a post-hoc analysis of HRQoL at week 26 and week 52 for study participants. These data without the reference to MCID or MID were presented in the previous submission and considered by the PBAC at the July 2023 meeting. The SF-6D is a new presentation of the SF-36 data not seen by the PBAC before. The data indicate that improvements in the quality of life of patients with AAV was higher (and statistically significant at week 52 for SF-36 the physical component score, SF-6D, EQ-5D health utility, and EQ-5D-5L visual analogue score) in patients in

[5] Heerspink H J L, Greene T, Tighiouart H, et.al. Change in Albuminuria as a Surrogate Endpoint for Progression of Kidney Disease: A Meta-Analysis of Treatment Effects in Randomised Clinical Trials. Lancet Diabetes Endocrinol. 2019; 7(2):128–39

the avacopan + SOC group compared to those in the GC + SOC group. For SF-6D and EQ-5D-5L visual analogue scale scores, improvements in both treatment groups at weeks 26 and 52 met the MID and for EQ-5D, only the avacopan group at week 52 met the MID.

**Rituximab**

6.33 A feasibility assessment for conducting an ITC between avacopan and fixed dose rituximab maintenance treatment in patients with AAV entering remission following rituximab induction was presented in the resubmission. The RCTs (MAINRITSAN, MAINRITSAN 2 and RITZAREM) which considered the use of rituximab as maintenance therapy were assessed against the ADVOCATE trial. The resubmission concluded that due to significant transitivity concerns (differences in maintenance regimens, outcome definitions, study population and design), limited sample size and lack of common comparator, the results from an ITC would be subject to bias and uncertainty. As such, the resubmission did not undertake an ITC.

6.34 The ESC agreed with the evaluation that the conclusions drawn from the feasibility assessment appeared reasonable as anchored indirect comparisons to compare avacopan and rituximab as maintenance therapies were not feasible between the ADVOCATE trial and any one of MAINRITSAN, MAINRITSAN 2, or RITAZAREM for a robust comparison. Furthermore, any unanchored indirect comparison was likely to be biased, and in the absence of individual patient data, would be contingent on making unfounded assumptions about trial participants, yielding highly uncertain results.

6.35 To account for the impact of adding rituximab to avacopan in maintenance in the economic evaluation, the probability of relapse from ADVOCATE was adjusted using the hazard ratio (HR) of 0.36 from the RITAZAREM trial where rituximab maintenance was shown to be superior to azathioprine in preventing disease relapse (Smith, Jayne et al. 2019). Table 9 presents the results from the RITAZAREM trial compared to the ADVOCATE trial. There are key differences between the two trials. In contrast to RITAZAREM which had a maintenance phase lasting 20 months, avacopan was only used as maintenance therapy for up to 6 months in ADVOCATE. RITAZAREM also excluded newly diagnosed participants from being eligible in the trial, whereas the ADVOCATE study population was mostly comprised of newly diagnosed patients (69.2%). Each trial also included different comparator arms, with rituximab being compared to azathioprine in RITAZAREM versus avacopan compared to prednisone in ADVOCATE. Additionally, the definition of remission in RITAZAREM differed from that in ADVOCATE. Despite these limitations, the evaluation considered RITAZAREM may provide the best available evidence of rituximab efficacy in the maintenance setting, reflecting Australian practice and population. The ESC considered the two-step approach involving the multiplication of probability by a hazard was associated with uncertainty (see paragraph 6.65). The lower rate of relapse in maintenance leads to the absolute treatment effect of avacopan being smaller when added to rituximab compared with azathioprine.

**Table 9: Comparison of outcomes presented in RITAZAREM and ADVOCATE trials**

| | RITAZAREM N = 170[a] | | ADVOCATE N = 330[b] | |
|---|---|---|---|---|
| **Trial duration** | 4 months induction and 20 months maintenance | | 6 months induction and 6 months maintenance, Median: 364 days | |
| **Eligible Participants** | Relapsing patients with a diagnosis of MPA or GPA aged over 15 years | | Newly diagnosed or relapsing patients with MPA or GPA | |
| **Trial primary outcome** | | | | |
| | **Rituximab n=85** | **Azathioprine n=85** | **Avacopan + SOC n=166** | **Prednisone + SOC n=164** |
| **Relapses [c], n (%)** | 38 (45%) | 60 (71%) | 16 (10%) [h] | 22 (21%) [h] |
| **Total number of relapses** | 85 | 89 | NA | NA |
| **Major [d]** | 11 | 28 | NA | NA |
| **Minor [e]** | 41 | 61 | NA | NA |
| **Overall HR for relapse (95% CI)** | 0.36 (0.18, 0.73) [f] | | 0.46 (0.25, 0.84) | |
| **Relapse-free survival rate at 24 months (95% CI)** | 0.85 (0.78, 0.93) | 0.61 (0.51, 0.73) | NA | NA |
| **Disease remission [g], n (%)** | NA | NA | 120 (72%) | 115 (70%) |
| **Sustained remission [g], n (%)** | NA | NA | 109 (66%) | 90 (55%) |

Source: Compiled during the evaluation

Abbreviations: GPA granulomatosis with polyangiitis; HR, hazard ratio; MPA microscopic polyangiitis; NA, not available; SOC, Standard of care

[a] Randomised sample

[b] One participant was excluded from the randomised sample due to not receiving prednisone

[c] Relapses were defined in ADVOCATE as a return of vasculitis activity on the basis of at least one major BVAS item, at least three minor BVAS items, or one or two minor BVAS items for at least two consecutive trial visits

[d] Major relapses were defined in RITAZAREM as the development of a new or recurrent major disease activity item using the BVAS

[e] Minor relapses were defined in RITAZAREM as any increase in disease activity that does not meet the definition of Major Relapse

[f] For major relapse

[g] Remission in ADVOCATE was defined as a BVAS of 0 and no receipt of glucocorticoids for 4 weeks before week 26 and week 52.

[h] Experiencing relapse after BVAS=0 was achieved

## *Comparative harms*

6.36 The resubmission presented safety outcomes from the ADVOCATE trial as per the previous submission. In addition, the resubmission newly presented an unpublished systematic review of GC use and its relationship to AEs, and newly presented early access program (EAP) data on 30 patients showing safety associated with some patients with longer term avacopan use.

6.37 Table 10 presents the safety outcomes in the ADVOCATE trial. The safety outcomes from the ADVOCATE trial are unchanged from the previous submission.

**Table 10: 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; CI, confidence interval; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; NR, not reported; SAE, serious adverse event; SOC, standard of care; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

[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.

Blue Shading indicates data previously seen by the PBAC

6.38 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 GC-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 urinary tract infection. 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.

6.39 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.

6.40 The ADVOCATE trial only provided safety evidence supporting the use of avacopan + SOC for treatment duration over 52 weeks. Given the relatively short duration of the treatment period, there is no safety evidence on the cumulative risk of reinduction or long-term safety data for maintenance treatment beyond this. There was no open-label extension study for the ADVOCATE trial. However, a randomised double-blind, placebo-controlled trial to evaluate the long-term safety and efficacy of avacopan in patients with AAV was recently registered on clinicaltrials.gov with an estimated completion date of 6 August 2031.

6.41 The resubmission included a systematic review of the burden of GC-associated AEs in the treatment of AAV (Attachment 4 of the resubmission) as new evidence to demonstrate the potential safety benefits of using avacopan to reduce exposure to GCs in patients with AAV. This was presented in the resubmission as an unpublished manuscript with authors funded by industry. Key findings from the review indicate that serious infections at 1-year were less common among patients treated with low-dose GC vs standard-dose GC (incidence rate ratio, 0.69; 95% CI, 0.52, 0.93)[6], treatment with GCs beyond 6 months was associated with a significantly higher risk of infection (0.42 infections/person-year [95% CI, 0.39–0.46] compared with those treated for up to 6 months (0.23 infections/person-year [95% CI, 0.2–0.25]) [7], and long term GC exposure might be an attribute of long-term AAV damage after 7 years of follow-up[8].

6.42 The resubmission included new evidence from the avacopan EAP as supportive real-world evidence to demonstrate the tolerability and safety of avacopan beyond 52 weeks (12 months). Among the 30 patients enrolled in the EAP (mean treatment duration of 11.5 months), eight experienced any AE. Among a subgroup of 19 patients

[6] Walsh M, Merkel PA, Peh C-A, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020; 382(7):622-31.

[7] McGregor JG, Hogan SL, Hu Y, et al. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol. 2012; 7(2):240-7.

[8] Robson J, Doll H, Suppiah R, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford). 2015; 54(3):471-81.

from the EAP who had longer-term use of avacopan (median duration: 17 months, range: 12-45 months), two patients experienced AEs (related to general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, vascular disorder). The additional evidence provides data for longer term use of avacopan, however this is based on small patient numbers thus data on the use of avacopan beyond 52 weeks remains limited.

## *Benefits/harms*

6.43 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 5). The ESC considered that this benefit was likely overstated given that SOC for maintenance therapy was not appropriate for the rituximab arm of the ADVOCATE trial, where there was no maintenance treatment.
- Approximately 15 fewer patients would experience endocrine or metabolic GC-related adverse events at Week 52 (Table 10).
- Approximately 9 fewer patients would experience dermatological GC-related adverse events at Week 52 (Table 10).

## *Clinical claim*

6.44 The resubmission described avacopan as superior compared to GC + SOC in terms of both efficacy and safety when administered for a treatment duration not exceeding 52 weeks per severe disease flare. The addition of the 52-week timeframe is the only difference from the previous submission claim.

6.45 The evaluation considered the therapeutic conclusion presented in the resubmission for effectiveness remained inadequately supported. The ESC considered the PBAC's previous conclusions remain valid: the magnitude of benefit that avacopan + 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; the clinical evidence provided was inadequate to assess remission at 52 weeks and did not support comparative assessment of use as maintenance therapy (para 7.1, avacopan, PSD, July 2023 PBAC Meeting).

6.46 The evaluation considered the evidence provided to support the broader benefits of avacopan when used as induction therapy or to support use as maintenance therapy over 12 months per severe disease flare remain uncertain.

- Although a statistically significant improvement in eGFR was observed at weeks 26 and 52 in patients with renal disease at baseline, improvements appeared to be

driven by the eGFR <30 mL/min/1.73m$^2$ subgroup and there is uncertainty in the benefit attributable to the group which compared avacopan to no maintenance therapy (para 7.11, avacopan, PSD, July 2023 PBAC meeting). It is also uncertain whether these benefits would translate to the proposed PBS population (para 6.24, avacopan, ESC advice, July 2023). The pre-PBAC response argued that the improvement in renal function as measured by eGFR at 52 weeks was acknowledged in international guidelines (EULAR and KDIGO) (see paragraph 6.24).

- Although patients in the avacopan + SOC arm achieved a 40% reduction in UACR sooner than those in the GC + SOC arm, the inference that this may have contributed to greater subsequent improvement in eGFR is uncertain. Further, translation of this outcome to long term benefits including improvement in eGFR is uncertain.
- Evidence to support avacopan use in the maintenance setting remains limited, given no use of avacopan in combination with rituximab was available and adjusting the benefit in the ADVOCATE trial using the hazard for rituximab compared to azathioprine from RITAZAREM was not considered reliable.

6.47 Post-hoc patient-reported health-related quality of life outcomes results appear to indicate that improvements in the quality of life of patients with AAV was higher (and statistically significant at week 52) in patients in the avacopan + SOC group compared to those in the GC + SOC group.

6.48 The ESC noted that a restriction to allow for a 12 month treatment cycle aligns with the ADVOCATE trial duration of use. However, the ESC advised that as the evidence supporting use in the maintenance setting was inadequate, the uncertainties associated with the benefits of avacopan outside of use as a strategy to reduce exposure to GCs during induction remained. The PBAC had also previously 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 (para 7.13, avacopan PSD, July 2023 PBAC meeting).

6.49 The resubmission described avacopan as superior in terms of safety compared to GC + SOC. In July 2023, the PBAC considered the claim of superior comparative safety 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 (para 7.13, avacopan PSD, July 2023 PBAC meeting). Supplementary evidence in the form of a systematic review (industry sponsored unpublished manuscript) provided by the resubmission appears to suggest that higher dose and longer exposure to GCs are likely to be associated with higher risk of Infection and long term AAV damage. Data from avacopan EAP provided data for longer term use of avacopan, however this was based on small patient numbers thus data on the use of avacopan beyond 52 weeks remains limited.

6.50 The PBAC considered that the claim of superior comparative effectiveness was uncertain but likely reasonable for induction therapy and was not adequately supported by the data for maintenance therapy.

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

## *Economic analysis*

6.52 The resubmission presented a modelled cost-utility analysis based on the randomised trial (ADVOCATE) directly comparing avacopan + SOC and GC + SOC. The PBAC previously determined that a resubmission for avacopan should be based on the benefits of reducing GC when used as induction therapy (para 7.16, PSD, avacopan, July 2023 PBAC meeting). The resubmission stated the sponsor was unable to proceed with a PBS listing for avacopan based on benefits of reducing GCs alone.

6.53 The resubmission argued that statistically significant improvements in renal function in the avacopan-treated arm compared with the prednisone arm were apparent at week 26 (i.e. in the induction phase when patients in the prednisone arm were still on background therapy with rituximab or cyclophosphamide). The resubmission argued improvement persists and remains statistically significant at week 52 and is confirmed as clinically meaningful by clinicians. The resubmission argued that it would be incorrect to attribute this improvement solely due to patients receiving "no therapy" in the prednisone arm of ADVOCATE. The economic model structure is therefore the same as the previous submission, however a number of key inputs have been updated.

6.54 The resubmission economic model continued to include avacopan benefits from clinical efficacy at achieving remission, renal disease progression based on eGFR rates, mortality (from AAV, ESRD, and infection from GC toxicity) and GC toxicity. The PBAC previously advised that 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 (para 7.16, PSD, avacopan, July 2023 PBAC meeting).

6.55 Key changes made in the resubmission model included:

- A reduced time horizon from 30 years to 20 years;
- An adjusted comparator that allows rituximab to continue into the maintenance phase of treatment;
- A maximum treatment duration reduced from 24 months to 12 months (9.6 months applied in model down from 25.8 months previously);
- The treatment waning of avacopan was reduced from 1 year to 6 months;
- A revised limit of 1 reinduction with avacopan down from up to 2 previously;
- An updated utility valuation set from Norman et al. (2023);

- An increase in the hazard ratio from 0.90 to 0.955 for unit change of eGFR and ESRD risk;
- A [redacted]% price reduction for avacopan — effective AEMP reduced from $[redacted] to $[redacted]; and
- A weighted comparison comprising of 50% of patients on cyclophosphamide + azathioprine and 50% on rituximab + rituximab to reflect current treatment guideline.

6.56 The key components of the economic evaluation comparing avacopan + SOC to GC + SOC are presented in Table 11.

**Table 11: Summary of model structure, key inputs and rationale**

| Component | Summary |
|---|---|
| Treatments | Induction: AVA+RTX or AVA+CYC<br>Maintenance: AVA+RTX (50%) or AVA+AZA (50%)<br>Vs<br>Induction: GC+RTX or GC+CYC<br>Maintenance: Tapered GC+RTX (50%) or Tapered GC+AZA (50%) |
| Time horizon | 20 years |
| Outcomes | QALYs |
| Methods used to generate results | Cohort state transition Markov model |
| Health states | 9 health states in total<br><br>Active disease, Remission (x3), Relapse (x3), ESRD, Death |
| Cycle length | 28 days |
| Transition probabilities or Allocation to health states (if partitioned survival model) | Active disease to relapse and remission: Proportions of patients in remission at week 26 and 52 from the ADVOCATE trial. Patients on rituximab between weeks 26-52 (in both treatment and control arms) have a lower relapse risk adjusted by HR of 0.36 from the RITAZAREM trial.<br><br>Relapse rate over time: Relapse rate after 2 years in remission is assumed to reduce to 1/5 of the relapse rate during the first 2 years. This is based on assumption.<br><br>Transition to ESRD: Based on renal outcomes (eGFR) from the ADVOCATE trial, the association between eGFR and the probability of ESRD using a pooled HR of 0.95 from Gercik et al. (2020) and Brix et al. (2018) and assumed a decrement of 10 mL/min decrease in eGFR for each subsequent relapse based on advice from clinical experts and data from Slot et al. (2003).<br><br>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 GC + SOC arm after 26 weeks of cessation of avacopan treatment. |

| Component | Summary |
|---|---|
| Health related quality of life | Health state utility values for the following health states were sourced from the ADVOCATE trial: Active disease = 0.819, Remission = 0.881, Relapse = 0.810. These have been updated from the previous model: Active disease = 0.702, Remission = 0.778, Relapse = 0.698.<br><br>For the ESRD health state, the following utility values were applied: Dialysis = 0.458 (resubmission'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).<br><br>The ESC noted that the utility value for the relapse health state had previously aligned with conservative management of ESRD which has a utility of 0.696. The updated relapse health state utility is now much higher at 0.810.<br><br>Decrement due to GC related infection = -0.2, based on utility decrements associated with lower respiratory infections associated with hospitalisations (Rothberg et al. 2003 and Chit et al. 2015) |
| Costs | The model incorporated costs related to induction and maintenance therapies, monitoring of the disease, and hospitalisation and clinic visits to cover serious adverse events. No changes were made in the way costs were applied in the model but values were revised as described in paragraph 6.75. |

Source: Tables3-1, 3-2. 3-3 & 3-13 of the resubmission
Abbreviations: AAV, ANCA associated vasculitis; AVA, anca-associated vasculitis; CYC, cyclophosphamide; DRG, Diagnosis related group; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GC, glucocorticoids; HR, hazard ratio; HTA, Health Technology Assessment; ICER, Incremental cost-effectiveness ratio; IV, Intravenous; IVIg, intravenous immune globulin; MBS, Medicare Benefits Schedule; NBA, National Blood Authority; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, pharmaceutical Benefits Scheme; QALYS, quality-adjusted life year; RTX. Rituximab; SOC, Standard of Care
Blue Shading indicates data previously seen by the PBAC

6.57 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 1 subsequent induction 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.

6.58 The model presented in the resubmission maintains the claim of clinical superiority of avacopan for achieving and maintaining remission as well as reducing the risk of developing end-stage renal disease (ESRD), compared to GCs + SOC. This difference is maintained throughout the time horizon of the model.

6.59 The resubmission included a revised treatment scenario where patients who received rituximab for induction therapy (50% of the cohort) continued to receive rituximab for maintenance therapy for Weeks 26 to 52. The resubmission noted that the use of rituximab for maintenance therapy resulted in a lower rate of relapse, resulting in a smaller difference in remission between the treatment arms and an increased ICER.

6.60 The proportion of patients on concomitant treatment with rituximab (50%) and cyclophosphamide (50%) was based on a treatment survey conducted by Australian and New Zealand Vasculitis Society (ANZVASC). Although the 50:50 split is more conservative than the 57% cyclophosphamide and 43% rituximab split as presented in the survey (based on Clinical Scenario 1[9]), it is uncertain, given that rituximab is now recommended in the EULAR Guidelines for maintenance therapy, is unrestricted on the PBS and appears to be more efficacious, whether the assumption will hold into the future. The ICER was sensitive to variations in the proportion of rituximab therapy (see Table 14). The previous submission did not consider rituximab as a maintenance therapy in the base case. The ESC noted the treatment split reported in the ANZVASC treatment survey varied depending on the clinical scenario. Rituximab was preferred by 86% of respondents if the scenario was varied from a 65 year old (as reported in Clinical Scenario 1) to a 35 year old patient. When the scenario was changed to the patient being 75 years old, with a diagnosis of localised breast cancer four years prior, 69% of respondents indicated they would preferentially use rituximab compared to cyclophosphamide. In addition, the ESC noted 16% of the 55 respondents to the ANZVASC treatment survey were from New Zealand where access to rituximab was more difficult than access in Australia. The ESC considered that difficulties in accessing rituximab may have resulted in lower reported use of rituximab in the responses from New Zealand participants. Noting these considerations along with guideline support for use and an unrestricted listing, the ESC considered a 50:50 split underestimated rituximab utilisation. The ESC considered rituximab would more likely be used in 70% to 90% of patients. The pre-PBAC response provided a revised base case that assumed 70% of patient receive rituximab (see paragraph 6.81).

6.61 The time horizon in the resubmission was revised from 30 years to 20 years. While this represents a reduction, the 20-year time horizon still requires substantial extrapolation from the ADVOCATE trial data, which had a study duration of 52 weeks.

6.62 The resubmission also reduced the avacopan treatment waning period from 12 months to 6 months following treatment cessation. The pre-PBAC response acknowledged the uncertainty in the duration of treatment waning and reduced this to 3 months in the revised base case provided in the response (see paragraph 6.81).

6.63 The duration of treatment in the resubmission was reduced from a maximum of 24 months in the previous submission to 12 months, and the number of reinductions was reduced to 1 (i.e., 2 inductions allowed). Maintenance therapy now reflects weeks 26 to 52 in the model.

[9] Clinical scenario 1 described a 65 year old female PR3-AAV patient with kidney and lung manifestations, significant kidney impairment (serum creatinine [sCr] 280mcmol/L, eGFR 20ml/min), who had undergone kidney biopsy demonstrating glomerular crescent formation with minimal interstitial fibrosis.

**Transition probabilities**

6.64 The transition probabilities presented in the resubmission for remission and for relapse for patients treated with cyclophosphamide and azathioprine remain unchanged.

6.65 To adjust the remission and relapse rates for patients who receive rituximab maintenance, a HR of 0.36 was applied to both arms of the model based on results of the RITAZREM trial (see paragraph 6.35). The evaluation considered RITAZAREM may provide the best available evidence to estimate this parameter in the absence of a direct and indirect comparison reflecting Australian practice and population. The ICER is sensitive to this parameter. Applying the lower bound of the 95% CI of the HR (0.18) increases the ICER to $75,000 to < $95,000 (12% increase from base case). The ESC considered multiplying a probability with a hazard ratio results in a statistical accumulation of errors, and the range of uncertainty makes this two-step approach unreliable. The ESC also advised that given the variance of a product is not equal to the product of the variances, the uncertainty of the two-step approach was greater than could be captured in the use of its confidence intervals in a sensitivity analysis (see Table 14). The pre-PBAC response argued that the approach taken to adjust for rituximab maintenance efficacy in the model is based on the best available evidence from the RITAZAREM trial and is considered to be a reasonable reflection of Australian general practice. The pre-PBAC response stated that this approach was previously accepted by National Institute for Health and Care Excellence (NICE).

6.66 The ESC noted that although the updated transition probabilities demonstrate a reduction in relapse rates between the arms compared to the previous submission, the relative difference between the two arms is maintained and the issue remains that the remission rate from the ADVOCATE trial (to which this adjustment is made) is highly uncertain.

6.67 The transition probabilities for ESRD, which have been adjusted to be slightly more conservative, still maintains superiority of avacopan in remission outcomes. This is inconsistent with previous PBAC determination that a resubmission for avacopan should be based on the benefits of reducing GC when used as induction therapy and that 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 (para 7.16, PSD, avacopan, July 2023 PBAC meeting).

6.68 The remission and relapse rates applied in the model were based on proportions of patients in remission at Weeks 26 and 52 from the ADVOCATE trial. The resubmission did not change the rate of remission achieved at Week 26 which maintained a difference in remission rates. This does not align with the trial results which demonstrated non-inferiority between the two treatment arms and did not demonstrate superiority. The pre-PBAC response provided a revised base case that removed the modelled difference in remission at 26 weeks (see paragraph 6.81).

6.69 The resubmission assumed that the treatment effect for the first induction was the same as for subsequent reinductions. Although the PBAC noted that avacopan would be suitable for reinduction therapy based on its mechanism of action (para 7.5, avacopan PSD, July 2023 PBAC meeting), the magnitude of treatment effect for reinductions is not available from the ADVOCATE trial data and remains uncertain.

6.70 The economic model incorporated eGFR data reported from the ADVOCATE trial to estimate the risk of ESRD for patients on avacopan + SOC and GC + SOC. Improvements in eGFR as reported in the trial were converted into the corresponding change in ESRD risk using an updated hazard ratio of 0.955 for ESRD per mL/min change in eGFR from baseline based on a pooled estimate from Gercik et al. (2020) (HR=0.9) and Brix et al. (2018) (HR=0.96). This is a more conservative estimate than the HR of 0.9 previously applied. Applying a HR of 0.9 decreases the ICER from $55,000 to < $75,000 /QALY gained (base case) to $35,000 to < $45,000/QALY gained (-37%). Although the updated HR represents a more conservative assumption in the model, the ICER remains sensitive to this outcome and there was significant uncertainty related to ESRD transition probabilities because:

- The transition probabilities applied for the Active disease to ESRD health state were calculated using baseline transition probabilities and the corresponding change in ESRD risk based on improvements in eGFR in the avacopan + SOC and GC + SOC arms of the ADVOCATE trial observed between Weeks 0 and 26 (5.8 mL/min and 2.9 mL/min, respectively). The PBAC previously noted that although there was an improvement in eGFR rates at both Week 26 and Week 52 for the population with renal disease, 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 significant difference in patients with renal disease. At that time 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 and that it was not clear how much of the benefit was attributable to the group which compared avacopan to no maintenance therapy (para 7.11, avacopan PSD, July 2023 PBAC meeting). The resubmission presented additional post hoc subgroup analyses of the ADVOCATE trial renal outcomes (eGFR and UCAR) but the original concerns remain. The change in eGFR is uncertain because the benefit was driven by patients with lower eGFR at baseline and the UCAR results whilst showing an initial benefit for avacopan failed to demonstrate statistical significance at 52 weeks. When the difference in eGFR response is removed in the model, the ICER increases to $95,000 to < $115,000 /QALY gained (+43% from base case).
- The resubmission assumed each subsequent relapse was associated with a 10 mL/min decrease in eGFR. This is the same as the previous model. The magnitude of eGFR decrement applied is uncertain because of the large standard deviation in the observed data from Slot et al. (2003). The ESC previously noted that the information from the clinicians referred to was not provided (para 6.53, avacopan PSD, July 2023 PBAC meeting), this was not addressed in the

resubmission. The ICER presented in the resubmission remains sensitive to this assumption, when a decrease in eGFR of 5 mL/min is applied the ICER increases to $75,000 to < $95,000/QALY gained (+10% from base case).

- Each subsequent relapse was subjected to the same decrement in eGFR and improvements in eGFR related to reinduction treatment. This assumption depends on several input parameters which are uncertain. These are the 10 mL/min magnitude of decrement applied for subsequent relapses and the difference in eGFR recovery (not established in the clinical evidence). The ESC noted the initial difference established from the ADVOCATE trial between arms is maintained and compounded over subsequent relapses in the economic model which favours the avacopan + SOC arm. The pre-PBAC response argued that it was appropriate to model a benefit in terms of eGFR based on data from the ADVOCATE trial and hence this approach was maintained in the revised base case (see paragraph 6.81).

**Extrapolation**

6.71 The resubmission reduced the treatment waning period to 26 weeks, compared to 52 weeks in the previous submission. The application of 26-week treatment waning is more conservative than the 52-week waning used in the previous submission. There are limited data on treatment waning as the follow-up period without avacopan treatment in the ADVOCATE trial was 56 days (8 weeks) which ESC considered unlikely to robustly inform a 12-month waning period (para 6.55, avacopan PSD, July 2023 PBAC meeting). The resubmission did not present any further evidence in support of the treatment waning model. The ICER is highly sensitive to this assumption. When time to treatment waning was reduced to 3-months, the ICER increased from $55,000 to < $75,000 /QALY gained (base case) to $75,000 to < $95,000/QALY gained (+24%). The structure of the model did not allow for changing of the linear shape of the waning function. The ESC noted the PSCR stated that while no data was provided to support treatment waning at 6 months, this was applied based on mechanism of action and clinical opinion. The data on treatment waning from the ADVOCATE trial was collected over an 8-week period and the ESC considered the application of 26-week treatment waning period was unlikely to be conservative.

6.72 The ESC noted the difference in survival between the avacopan + SOC and GC + SOC arms appear to be small (<1%) in the first 5 years. This small difference increased with progression through the model however relative to the results presented in the previous submission the difference in death rate is far smaller. For example, in the previous submission the difference in death rate in the avacopan arm compared to the GC + SOC was approximately 15% by Year 15, in the current submission by year 15 the difference in mortality rate is <3%. This is likely be due to the reduction in the difference in the portion of patients entering ESRD state.

**Utility values**

6.73 The resubmission presented an updated EQ-5D-5L utility value set for Australia from Norman et al. (2023). 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 was reasonable and the use of non-treatment specific health state values minimises the risk of double counting.

6.74 The resubmission applied a decrement of 0.2 for the occurrence of any GC-related infections. This was revised from the previous submission (0.1 decrement). The resubmission considered 0.2 to be a more reasonable assumption as it was based on literature estimates for lower respiratory infections associated with hospitalisation from Rothberg et al. (2003) and Chit et al. (2015). It is unclear whether utility values for lower respiratory infection were appropriate for GC related infection. The updated utility values were favourable to avacopan, decreasing the updated utility decrement from 0.2 to 0.1 increased the ICER from $55,000 to < $75,000 /QALY gained to $75,000 to < $95,000/QALY gained (+13%). The ESC considered that a utility decrement of 0.2 for any GC-related infections was high in the context of a condition that has a high existing disease burden (see paragraph 4.1). The pre-PBAC response provided a revised base case that applied a utility decrement of 0.1 for any GC-related infections (see paragraph 6.81).

**Costs**

6.75 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.

6.76 Several costs were revised and are outlined below:

- The AEMP of avacopan has been reduced to $ (% reduction), which equates to $ per capsule. The pre-PBAC response offered a further price to an AEMP of $.
- Costs for medications (rituximab, cyclophosphamide, azathioprine), monitoring, ERD and terminal care have been updated to September 2023 values.
- The treatment duration of avacopan has been revised to a maximum 12 month duration.
- For the combined arm (i.e. CYC/RTX) the weighting is 50% cyclophosphamide, 50% rituximab. The pre-PBAC response provided a revised base case that assumed 70% of patient receive rituximab.
- The cost of rituximab has been added in cycles 7 to 13 for the rituximab maintenance scenario.
- The base case assumes 1 reinduction with avacopan for patients that relapse. This is applied as the cost of induction plus a one-off cost of maintenance therapy. This

is estimated at 4.0 months duration (i.e. 6 months induction plus 4.0 months maintenance) to align with the average treatment duration of avacopan.

- Hospital costs were updated to reflect 2020/2021 weights.
- Average cost per infection was updated for each arm.

6.77 Table 12 summarises key drivers of the economic model.

**Table 12: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case: $[redacted][5]/QALY gained |
|---|---|---|
| Time horizon | 20 years | Very high, favours avacopan<br>Use of 15 and 10 year time horizons increase the ICER to $[redacted][1]/QALY (+20%) and $[redacted][2]/QALY (+87%) respectively |
| Difference in remission and relapse rate | 26 weeks: avacopan + SOC 72.5% and GC + SOC 70.1%<br>52 weeks avacopan + SOC 65.7% and GC + SOC 54.9% | Very high, favours avacopan<br>When the difference in relapse and remission rate is equal to that of GC + SOC the ICER increases to $[redacted][2]/QALY (+93%) |
| Waning | Treatment effect waned 6-months following cessation of treatment | High, favours avacopan<br>When the treatment effect was stopped at the cessation of treatment the ICER increased to $[redacted][3]/QALY (+56%) |
| Proportion of infections avoided | 72.1% for those in the avacopan arm | High, favours avacopan<br>When no effect was assumed the ICER increased to $[redacted][2]/QALY (+82%) |
| HR applied to corresponding change in eGFR | HR=0.955, pooled data from Gercik et al. (2020) and Brix et al. (2018) | High, uncertain and could favour either.<br>Using the HR of 0.90 applied in the previous submission decreases the ICER to $[redacted][4] (-37%) using the 0.96 from Brix et al. (2018) increased the ICER to $[redacted][5]/QALY (+3%) |

Source: Compiled during the evaluation using information from Table 3-35, p163 of the resubmission and outputs from Attachment 26
Abbreviations :eGFR, estimated glomerular filtration rate; GC, glucocorticoid; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SOC, Standard of care.
*The redacted values correspond to the following ranges:*
[1] *$75,000 to < $95,000*
[2] *$115,000 to < $135,000*
[3] *$95,000 to < $115,000*
[4] *$35,000 to < $45,000*
[5] *$55,000 to < $75,000*

6.78 The results of the economic evaluation are presented in Table 13. The resubmission did not present a stepped economic evaluation. This would have been informative to demonstrate the impact of the transformation of costs and outcomes to include multiple relapses, re-inductions with avacopan and treatment over the 20-year time horizon.

**Table 13: Results of the economic evaluation**

| | Avacopan + SOC | GC + SOC | Increment |
|---|---|---|---|
| **Outcome: Life year (LY)** | | | |
| **Azathioprine scenario** | | | |
| Costs | $ | $244,862 | $ |
| IYs | 9.21 | 9 | 0.2 |
| Incremental cost/extra LY gained | | | $ [1] |
| **Rituximab scenario** | | | |
| Costs | $ | $232,598 | $ |
| IYs | 9.27 | 9.15 | 0.15 |
| Incremental cost/extra LY gained | | | $ [2] |
| **Weighted ICER (50:50): Incremental cost/extra LY gained** | | | **$** [3] |
| **Outcome: Quality-adjusted life year (QALY)** | | | |
| **Azathioprine scenario** | | | |
| Costs | $ | $244,862 | $ |
| QALYs | 7.35 | 6.98 | 0.37 |
| Incremental cost/extra QALY gained | | | $ [4] |
| **Rituximab scenario** | | | |
| Costs | $ | $244,862 | $ |
| QALYs | 7.45 | 7.16 | 0.29 |
| Incremental cost/extra QALY gained | | | $ [1] |
| **Weighted ICER (50:50): Incremental cost/extra QALY gained** | | | **$** [5] |

Source: Table 3-31, p160 of the resubmission

Abbreviations: GC, Glucocorticoids; ICER; Incremental cost-effectiveness ratio; LY, life-year; QALY, quality adjusted life year; SOC, standard of care

*The redacted values correspond to the following ranges:*

[1] *$75,000 to < $95,000*

[2] *$155,000 to < $255,000*

[3] *$115,000 to < $135,000*

[4] *$45,000 to < $55,000*

[5] *$55,000 to < $75,000*

6.79 Results of the key univariate sensitivity analysis are presented in Table 14.

**Table 14: Results of the univariate sensitivity analysis**

| Description | Incremental cost | Incremental QALYs | ICER | % change in ICER |
|---|---|---|---|---|
| Base case | $ | 0.33 | [1] | - |
| **Remission rate (base case: 26 weeks, AVA 72.3% GC + SOC 70.1%; 52 weeks, AVA 65.7% GC + SOC 54.9%; 60 weeks AVA 62% GC + SOC 50.6%)** | | | | |
| Equal to GC + SOC values at 26 weeks (no difference) [a] | $ | 0.33 | [1] | % |
| Equal to GC + SOC values at all stages (no difference) [a] | $ | 0.23 | [2] | % |
| **HR for rituximab maintenance adjustment (base case 0.36, RITAZAREM trial (Smith et al. (2019))** | | | | |
| 95% CI lower bound (0.18) [a] | $ | 0.32 | [3] | % |
| 95% CI upper bound (0.66) [a] | $ | 0.35 | [1] | -% |
| **Time horizon (base case 20 years)** | | | | |
| 10 years [a] | $ | 0.20 | [2] | % |
| 15 years | $ | 0.28 | [3] | % |
| 30 years | $ | 0.36 | [1] | -% |
| **Discount rate (base case 5%)** | | | | |
| 3.50% | $ | 0.38 | [1] | -% |
| 0% | $ | 0.53 | [4] | -% |

| Description | Incremental cost | Incremental QALYs | ICER | % change in ICER |
|---|---|---|---|---|
| **Treatment waning (base case 6 months)** | | | | |
| No waning | -$ | 0.74 | Dominant | NA |
| Immediate waning | $ | 0.27 | [redacted] | [redacted]% |
| Wane after 3 months | $ | 0.30 | [redacted] | [redacted]% |
| Wane after 1 year | $ | 0.39 | [redacted] | -[redacted]% |
| **Relapse rate adjustment after 2 years in remission (base case 0.2)** | | | | |
| 0.1 [a] | $ | 0.34 | [redacted] | -[redacted]% |
| 0.3 [a] | $ | 0.32 | [redacted] | [redacted]% |
| **Proportion of infections avoided through avacopan (base case 73.1%)** | | | | |
| 0% [a] | $ | 0.26 | [redacted] | [redacted]% |
| +10% [a] | $ | 0.34 | [redacted] | -[redacted]% |
| -10% [a] | $ | 0.32 | [redacted] | [redacted]% |
| **ESRD parameters (base case 10 mL/min eGFR drop on relapse, HR improvement (0.955)** | | | | |
| 5 mL/min eGFR drop on relapse | $ | 0.31 | [redacted] | [redacted]% |
| 20mL/min eGFR drop on relapse | $ | 0.37 | [redacted] | -[redacted]% |
| Brix et al. 2018 HR improvement in eGFR (0.96) | $ | 0.32 | [redacted] | [redacted]% |
| Gercik et al. 2020 HR improvement in eGFR (0.90) | $ | 0.42 | [redacted] | -[redacted]% |
| Avacopan eGFR recovery equal to GC + SOC in avacopan arm | $ | 0.27 | [redacted] | [redacted]% |
| **Utility (Base case, remission 0.881, active disease 0.819, relapse 0.810, weighted dialysis 0.458, transplant 0.712, conservative management 0.810)** | | | | |
| Treatment specific utilities (avacopan: remission 0.889; active disease 0.819, relapse 0.864. GC + SoC: remission 0.873, active disease 0.818 relapse 0.787) | $ | 0.37 | [redacted] | -[redacted]% |
| Utility values from the previous submission (remission 0.842, active disease 0.780 and relapse 0.760) | $ | 0.32 | [redacted] | [redacted]% |
| EQ-5D-3L instrument used [a] | $ | 0.29 | [redacted] | [redacted]% |
| Utility decrement 0.1 for acute infection (base case 0.2) [a] | $ | 0.29 | [redacted] | [redacted]% |
| ESRD utility for dialysis and transplant from Wyld et al. (2012) [a] | $ | 0.28 | [redacted] | [redacted]% |
| **Rituximab maintenance weighting (base case 50%)** | | | | |
| 100% rituximab use [a] | $ | 0.29 | [redacted] | [redacted]% |
| 90% rituximab use | $ | 0.30 | [redacted] | [redacted]% |
| 70% rituximab use | $ | 0.31 | [redacted] | [redacted]% |
| 43% rituximab use [a] | $ | 0.34 | [redacted] | -[redacted]% |
| 30% rituximab use | $ | 0.35 | [redacted] | -[redacted]% |
| 0% rituximab use [a] | $ | 0.37 | [redacted] | -[redacted]% |
| **Multivariate sensitivity analyses** | | | | |
| **Scenario 1: Rituximab maintenance weighting (70%)** | | | | |
| Remission rate equal to GC + SOC values at 26 weeks (no difference) | $ | 0.31 | [redacted] | [redacted]% |
| As above + utility decrement 0.1 for acute infection | $ | 0.27 | [redacted] | [redacted]% |
| As above + treatment waning after 3 months | $ | 0.23 | [redacted] | [redacted]% |
| As above + avacopan eGFR recovery equal to GC + SOC | $ | 0.17 | [redacted] | [redacted]% |

| Description | Incremental cost | Incremental QALYs | ICER | % change in ICER |
|---|---|---|---|---|
| **Scenario 2: Rituximab maintenance weighting (90%)** | | | | |
| Remission rate equal to GC + SOC values at 26 weeks (no difference) | $ | 0.28 | [3] | % |
| As above + utility decrement 0.1 for acute infection | $ | 0.25 | [5] | % |
| As above + treatment waning after 3 months | $ | 0.21 | [8] | % |
| As above + avacopan eGFR recovery equal to GC + SOC | $ | 0.15 | [9] | % |

Source: Table 3-35, p162 of the resubmission and complied during the evaluation and *updated during the preparation of the ESC advice*
Abbreviations: AAV, ANCA-associated vasculitis; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; GC, glucocorticoids; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; QALY; quality-adjusted life year; SOC, standard of care
[a] Completed as part of the evaluation
*The redacted values correspond to the following ranges:*
*[1] $55,000 to < $75,000*
*[2] $115,000 to < $135,000*
*[3] $75,000 to < $95,000*
*[4] $25,000 to < $35,000*
*[5] $95,000 to < $115,000*
*[6] $35,000 to < $45,000*
*[7] $45,000 to < $55,000*
*[8] $135,000 to < $155,000*
*[9] $155,000 to < $255,000*

6.80 The ESC considered that, with the changes to the economic model outlined in paragraph 6.55, the model was somewhat more conservative in some parameters (e.g. hazard ratio for unit change of eGFR and ESRD risk, price and treatment duration), less conservative in others (e.g. utility decrement for acute in infection) and unchanged in many. The ESC considered that the base case rituximab maintenance weighting was unlikely to reflect clinical practice and noted that increasing this input to 70% or 90% rituximab use increased the ICER from a base case of $55,000 to < $75,000 /QALY to $75,000 to < $95,000/QALY or $75,000 to < $95,000/QALY respectively. The ESC noted that the ICER further increased in the multivariate analyses incorporating a rituximab maintenance weighting of 70% or 90% (see Table 14). Overall, the ESC advised that despite the changes to the economic model in the resubmission the ICER remained highly uncertain and inadequately supported by the clinical evidence.

6.81 The pre-PBAC response acknowledged the concerns raised by the ESC and provided a revised base case that incorporated a rituximab maintenance weighting of 70%, a remission rate equal to GC + SOC values at 26 weeks (i.e. no difference), a utility decrement of 0.1 for any GC-related infections and treatment waning for avacopan after 3 months. At the AEMP offered in the pre-PBAC response ($), the revised base case resulted in an ICER of $55,000 to < $75,000 /QALY.

## *Avacopan cost/patient/course*

6.82 The average drug cost per course of treatment of avacopan (i.e., cost per relapse event) was $ (estimates from the economic model based on average duration of

treatment of 9.6 months). This represents a [redacted]% reduction in the cost per year presented in the previous submission ($[redacted]). This was due to a lower proposed price for avacopan and a maximum 12-month treatment duration.

6.83 A comparison of avacopan use between the trial setting, the economic model and the financial estimates is presented in Table 15.

**Table 15: Drug cost per patient for proposed and comparator drugs**

| | 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 6 months (maintenance) | 30 mg twice daily for up to 12 months |
| Avacopan re-induction | No | 1 | 1 |
| Mean total duration of treatment | 10.0 months | 9.6 months | 9.6 months |
| Compliance | 86.4% | 86.4% | 86.4% |
| Cost/patient/course | $[redacted][a] | $[redacted][a] | $[redacted][a] |

Source: Compiled during the evaluation from Attachment 26 – Avacopan CE model & Attachment 29 – Avacopan Section 4 financial model
Abbreviations: mg, milligram
a DPMQ multiplied by compliance rate multiplied by length of course.

6.84 The pre-PBAC response offered a [redacted]% price reduction from an AEMP of $[redacted] to an AEMP of $[redacted].

## *Estimated PBS usage & financial implications*

6.85 This resubmission was considered by DUSC.

6.86 The July 2023 submission was considered by DUSC with the subcommittee advising the estimates were reasonable if Population 3 was removed which had a substantial amount of uncertainty (para 6.80, avacopan PSD, July 2023 PBAC Meeting). The July 2023 submission used an epidemiological approach and identified four patient populations that would be eligible for avacopan: (1) newly diagnosed; (2) relapsed; (3) re-induction; and (4) grandfathered patients (para 6.73, avacopan PSD, July 2023 PBAC Meeting). In July 2023, 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. At that time, 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 (para 7.15, avacopan PSD, July 2023 PBAC Meeting).

6.87 The resubmission claimed that further data analysis subsequent to the July 2023 PBAC submission indicated that a larger number of AAV patients are likely to be prevalent in Australia, and therefore treated, than estimated in the previous submission. The resubmission presented an epidemiological approach using a revised financial model. The resubmission applied a different approach to estimating the eligible population compared to the previous submission. The resubmission used a new data source

which substantially increased the estimated number of patients treated with avacopan. A revised AEMP for avacopan was also applied in the resubmission.

6.88 Table 16 provides a summary of the key inputs and issues in the resubmission financial estimates. With the exception of the avacopan compliance rate all inputs are changed from the previous submission. DUSC comments on the key inputs for the resubmission financial estimates are included in the table.

**Table 16: Key inputs for financial estimates**

| Data | Value | Source | Commentary on the submission | DUSC Comments |
|---|---|---|---|---|
| **Eligible population** | | | | |
| Incident patients | Yr 1: 997<br>Yr 2: 1,011<br>Yr 3: 1,026<br>Yr 4: 1,040<br>Yr 5: 1,054<br>Yr 6: 1,068 | QHAPDC admission data from GPA and MPA 2014-2019 (incidence rate 0.0036%) | The July 2023 submission used an incidence rate of 0.00134% from Ormerod et al. (2008). The updated estimates for number of incident patients have more than doubled (128% increase) from that presented in the previous submission. The PBAC had previously 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" (para 7.15, avacopan PSD, July 2023 PBAC Meeting). | DUSC commented that the QHAPDC admission data reports the number of patients treated per year, rather than identifying initial patients. DUSC considered this reflects prevalence rather than incidence. DUSC noted the commentary included a comparison to the PBS 10% sample, and that the treated patients in the 10% sample were similar to the numbers in the QHAPDC admission data. DUSC considered it was not appropriate to use a prevalent population and follow the same logic as the original submission, as it was based on an incident population.<br><br>DUSC considered that the assumption that 50% of patients were treated with rituximab was underestimated and it may be more appropriate to assume 80% of patients were treated with rituximab.<br><br>DUSC considered the number of incident patients may be slightly higher than the previous submission estimated but not three times higher as estimated in the resubmission. |
| Relapse patients eligible for avacopan | Yr 1: [redacted]<br>Yr 2: [redacted]<br>Yr 3: [redacted]<br>Yr 4: [redacted]<br>Yr 5: [redacted]<br>Yr 6: [redacted] | 10% relapse rate applied based on Rituximab PSD March 2015 PBAC meeting | This is reasonable and aligns with DUSC advice which considered that 10% was reasonable for years 2-5 (para 6.27, rituximab PSD, March 2015 PBAC meeting). | DUSC commented that this was considered reasonable for the previous submission, but as the resubmission used hospital admissions to estimate patients, relapsed patients were included and the 10% relapse rate led to double counting of patients. |

| Data | Value | Source | Commentary on the submission | DUSC Comments |
|---|---|---|---|---|
| Total patients | Yr 1: [redacted]<br>Yr 2: [redacted]<br>Yr 3: [redacted]<br>Yr 4: [redacted]<br>Yr 5: [redacted]<br>Yr 6: [redacted] | Addition of incident and relapse patients | The approach of adding incident and relapse patients is reasonable. However, these estimates represent a substantial increase compared to that presented in the previous submission. | DUSC considered the main reason for the substantial increase in estimates was because the sponsor applied a prevalence rate to an incidence approach, which is incorrect. |
| **Treatment utilisation** | | | | |
| Uptake rate | Yr 1: 50%<br>Yr 2: 65%<br>Yr 3: 80%<br>Yr 4: 85%<br>Yr 5: 90%<br>Yr 6: 90% | Assumption based on clinical guidance + avacopan PSD July 2023 PBAC meeting | The resubmission revised the uptake rate in Year 2 from 50% to 65%. This was consistent with DUSC advice. "DUSC considered that the uptake rate in Year 2 could be increased to 65% to resemble the rituximab trajectory more closely" (Table 17, avacopan PSD, July 2023 PBAC meeting). | DUSC agreed this was reasonable. |
| Duration of treatment | 9.6 months (287.85 days) | Updated proposed restriction and economic model | The 9.6 months is based on the updated average treatment duration in the economic model. | DUSC considered this was reasonable. |
| Avacopan compliance | 86.4% | ADVOCATE trial | This is appropriate | |
| Number treated | Yr 1: [redacted]<br>Yr 2: [redacted]<br>Yr 3: [redacted]<br>Yr 4: [redacted]<br>Yr 5: [redacted]<br>Yr 6: [redacted] | Total patients multiplied by uptake rate | This approach is reasonable, however noting that these estimates represent a substantial increase compared to that presented in the previous submission. | DUSC reiterated that the approach that led to the substantial increase in treated patients was incorrect. |
| Scripts dispensed | Yr 1: [redacted]<br>Yr 2: [redacted]<br>Yr 3: [redacted]<br>Yr 4: [redacted]<br>Yr 5: [redacted]<br>Yr 6: [redacted] | Calculated based on number treated, assumed duration of treatment and avacopan compliance | This calculation has been verified. | DUSC considered this was reasonable. |
| **Costs** | | | | |
| Proposed medicine (effective) | AEMP<br>$[redacted]<br>DPMQ<br>$[redacted] | Effective AEMP | The revised effective AEMP represents a [redacted]% reduction from the July 2023 effective AEMP. | |
| Comparator (prednisone) | 1 mg: $15.38 [a]<br>5 mg: $15.76 [a]<br>25 mg: $16.59 [a] | PBS item numbers: 1934T, 1935W, 1936X | This is appropriate | DUSC considered this was reasonable. |
| Patient copayment for avacopan | PBS $27.71<br>RPBS $6.60 | PBS statistics for rituximab (13101M, 13095F) | The copayment for avacopan on the PBS has been updated from the | DUSC noted that the PBS copayments from 1 January 2024 were $31.60 for General |

| Data | Value | Source | Commentary on the submission | DUSC Comments |
|---|---|---|---|---|
| | | | previous submission and appears to reflect 1 January 2023 rates weighted by rituximab use by general patients and concession. | and $7.70 for Concessional services. |

Source: Compiled during the evaluation based on information sourced from Section 4.1, 4.2 and 4.3 of the submission.
Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, Dispensed Price for Maximum Quantity; DUSC, Drug Utilisation Sub Committee; GPA, granulomatosis polyangiitis; MPA, microscopic polyangiitis; PBAC, Pharmaceutical Benefits Advisory Committee PBS, Pharmaceutical Benefits Scheme; PSD, public summary document; RPBS, Repatriation Pharmaceutical Benefits Scheme; QHAPDC, Queensland Hospital Admitted Patient Data Collection
a DPMQ prices
Blue shading indicates data previously seen by the PBAC.
*The redacted values correspond to the following ranges:*
[1] *500 to < 5,000*
[2] *< 500*
[3] *5,000 to < 10,0004*

6.89 The resubmission presented revised incidence estimates based on data from the Queensland Hospital Admitted Patients Data Collection (QHAPDC), an administrative data collection maintained by Queensland Health. The number of distinct patients admitted to public and private hospitals in Queensland and coded with principal or other ICD-10-AM diagnosis codes for GPA (M31.3) or MPA (M31.7) per calendar year between 2014 and 2019 were obtained. These estimates are uncertain because:

- The use of 'other' ICD-10-AM codes (rather than just the primary diagnosis category) for locating GPA or MPA may identify patients who would not be eligible for avacopan treatment as they presented to hospital with a different primary complaint .
- It is unclear whether the ICD-10-AM codes used to classify cases of GPA and MPA are consistent with the requested restriction and the proposed PBS listing will allow treatment under specialist care without the requirement of a hospital admission.
- The resubmission claimed to calculate the number of distinct patients admitted per calendar year. This would allow the same patient to be represented in multiple years. The PSCR agreed with the evaluation that the same patient could be represented in multiple years in the dataset and argued that this was appropriate in order to capture relapsing patients who would be eligible for reinduction with avacopan. DUSC agreed with the PSCR that relapsing patients were included in the QHAPDC dataset, and considered that the 10% relapse rate lead to double counting of patients in the resubmission.

6.90 The revised incidence estimates represent a substantial increase (+128%) in the estimated number of patients treated with avacopan compared to the previous submission. In the previous submission, a study by Ormerod et al. (2008) was used to establish the incident and prevalent population, which was consistent with the March 2015 rituximab PSD. DUSC previously considered that the inputs derived from Ormerod et al. (2008) were likely appropriate given their alignment with previous

rituximab utilisation (Table 17, avacopan PSD, July 2023 PBAC meeting). The PSCR stated that the incidence estimate used in the previous submission was taken from the Ormerod et al. (2008) study which was based on data to 2005. The PSCR argued the prevalence estimate derived from the QHAPDC is more recent and represents admissions in the public health system in an entire state over multiple years. The PSCR stated that extrapolation of this data provides a more recent and accurate representation of patients hospitalised for AAV in Australia. DUSC commented that the QHAPDC admission data reports the number of patients treated per year, rather than identifying initial patients. DUSC agreed with the PSCR that this reflects a prevalence estimate rather than an incidence estimate.

6.91 The resubmission stated it validated the revised estimates using a PBS 10% sample, which provided an estimate of the number of unique patients treated with rituximab for GPA or MPA in Australia per year from 2017-2022. The resubmission assumed that 50% of patients were treated with rituximab and 50% with cyclophosphamide and therefore the number of patients was doubled. The AAV incidence rate from the 10% PBS sample was calculated at 0.0039%, slightly higher than the incidence rate used in the resubmission from the QHAPDC (0.0036%). There is uncertainty in the approach taken to determine this estimate. The DUSC Secretariat provided an analysis of PBS data on rituximab initiators and total treated patients between 2016 and 2022 as part of the evaluation of the July 2023 submission. These estimates were substantially lower than those provided in the resubmission's 10% PBS sample for 2019-2022 and are likely a better estimate of incidence. The 10% PBS sample analysis presented may be based on patient initiators (including reinduction) rather than incidence cases. The PSCR noted that in 2021 the sponsors 10% sample analysis estimated 490 patients treated with rituximab versus 489 patients treated annually in the DUSC Secretariat analysis. DUSC agreed that the prevalent treated patients in the 10% sample were similar to the numbers of treated patients in the data provided by the DUSC Secretariat based on the 100% PBS sample but considered this did not align with the incidence approach taken by the resubmission.

6.92 Table 17 summarises the estimated eligible population and the net cost to PBS/RPBS of listing avacopan, based on the submission effective DPMQ of $.

**Table 17: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Total patients treated** | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| **Total patients treated (July 2023 submission)** | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| **Script numbers** | | | | | | |
| PBS | [redacted][1] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| RPBS | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| **Total script numbers** | [redacted][1] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| **Cost** | | | | | | |
| Cost to PBS | [redacted][4] | [redacted][5] | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] |
| Less co-payments | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] |
| Net cost to PBS | [redacted][4] | [redacted][5] | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] |
| Cost to RPBS | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] |
| Less co-payments | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] |
| Net cost to RPBS | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] |
| **Net cost to PBS/RPBS** | [redacted][4] | [redacted][5] | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] |
| **Net cost to PBS/RPBS (July 2023 submission)** | [redacted][4] | [redacted][4] | [redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] |

Source: Table 4-28, p181 of the resubmission
Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Schedule of Pharmaceutical Benefits
Blue shading indicates data previously seen by the PBAC.
*The redacted values correspond to the following ranges:*
[1] *500 to < 5,000*
[2] *< 500*
[3] *5,000 to < 10,000*
[4] *$10 million to < $20 million*
[5] *$20 million to < $30 million*
[6] *$30 million to < $40 million*
[7] *net cost saving*
[8] *$0 to < $10 million*

6.93 The resubmission estimated avacopan use to cost the PBS/RPBS $10 million to < $20 million in Year 1, increasing to $30 million to < $40 million in Year 6, totalling $100 million to < $200 million over the 6 years. In the previous submission, the estimated cost of avacopan use to the PBS/RPBS was $10 million to < $20 million in Year 1 increasing to $20 million to < $30 million in Year 6, totalling $100 million to < $200 million. This represents a 27% increase in the estimated cost from the previous submission, despite the price reduction, driven by the increase in incidence.

6.94 DUSC considered the estimates presented in the resubmission to be overestimated. The main issues were:

- The resubmission used prevalence data and applied it as a rate of incidence. This was incorrect and overestimated the number of treated patients.
- The assumption that 50% of patients were treated with rituximab was underestimated and it may be more appropriate to assume 80% of patients were treated with rituximab.
- Relapsed patients were included in the hospital admissions data, and the application of a 10% relapse rate should be removed.

- The Queensland Hospital Admitted Patients Data Collection (QHAPDC) estimates are uncertain because the use of 'other' ICD-10-AM codes (rather than just the primary diagnosis category) for locating GPA or MPA may identify patients who would not be eligible for avacopan treatment, lack of clarity whether the ICD-10-AM codes used to classify cases of GPA and MPA are consistent with the requested restriction and possible representation of same patient across multiple years.

6.95 The pre-PBAC response acknowledged that applying a 10% relapse rate may result in double counting of patients across years when using the QHAPDC estimates but maintained the use of QHAPDC data was appropriate. In addition, the pre-PBAC response proposed a reduction in the uptake estimates across the first 3 years of listing based on data from countries that have already received avacopan. The pre-PBAC response provided revised financial estimates that incorporated an AEMP of $, removed the 10% relapse rate and decreased the uptake rate in Year 1 to Year 3 (Year 1: 50% to 25%, Year 2: 50% to 45%, Year 3: 80% to 75%). The revised financial estimates resulted in an estimated < 500 patients receiving avacopan in Year 1 at a cost to the PBS/RPBS of $0 to < $10 million, increasing to 500 to < 5,000 patients in Year 6 at a cost of $20 million to < $30 million.

### *Quality Use of Medicines*

6.96 The resubmission did not present a quality use of medicines (QUM) section. This may be inappropriate given that this is a new medication. Further, DUSC also considered 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 (para 6.82, avacopan PSD, July 2023 PBAC meeting).

### *Financial Management – Risk Sharing Arrangements*

6.97 No risk sharing arrangements were proposed in the resubmission. The pre-PBAC response offered a risk sharing arrangement with a % cap alongside amendments to the financial estimates as described in paragraph 6.95.

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

## 7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (telephone/online) listing of avacopan for induction therapy for the treatment of severe active granulomatosis with polyangiitis (GPA) and severe active microscopic polyangiitis (MPA) in combination with a regimen of rituximab or cyclophosphamide. The PBAC was satisfied that avacopan provides, for some patients, a significant improvement in efficacy over glucocorticoids (GCs). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of avacopan would be acceptable at the price proposed in the pre-PBAC response and if the

following measures were implemented to contain risks associated with the cost of the drug to the PBS:

- a risk sharing arrangement with a % cap based on amended July 2023 financial estimates; and
- Removal of maintenance and reinduction from the restriction treatment phase.

7.2 The PBAC noted the comments from individuals 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 regarding the potential for improvement in quality of life and reduced toxicity compared with current standard of care (SOC).

7.3 The PBAC reaffirmed its July 2023 advice that there was a clinical need for treatments that allow avoidance of high, cumulative GC use in this condition (para 7.3, avacopan PSD, July 2023 PBAC Meeting). The PBAC considered the clinician presentation in the sponsor hearing informative as it suggested avacopan, for induction, provided a benefit in reducing GC use along with potential earlier onset of renal improvement for patients at high risk of organ damage, especially for those whose eGFR is at the lower end of the range. The PBAC noted this was supported by the clinical evidence from the ADVOCATE trial and by the KDIGO (2024) guidelines.

7.4 With respect to the proposed restriction the PBAC advised:

- An Authority Required (telephone/online) listing was appropriate to allow monitoring of a maximum 12-month duration of treatment per cycle and the requirement for concomitant therapy;
- The treatment phase of the restriction state 'induction treatment' only. The PBAC acknowledged that in the context of the avacopan restriction, concomitant therapy in those induced with cyclophosphamide may include oral azathioprine or mycophenolate mofetil after week 13 or 14 according to the regimen specified in the drugs approved Product Information. It was acknowledged the definition of maintenance of remission proposed in the resubmission was meant to represent the treatment period of 6–12 months following induction; however, it was considered that given maintenance therapy with avacopan is not recommended in KDIGO (2024) and EULAR (2022) treatment guidelines that this wording should not be used in the PBS restriction;
- While there is no clinical evidence presented to inform reinduction, the PBAC reiterated its July 2023 advice that avacopan would be suitable for reinduction therapy based on its mechanism of action (para 7.5, avacopan PSD, July 2023 PBAC meeting). This was also supported in the sponsor hearing. However, the Committee advised that reinduction should not be included in the treatment phase, and that the extent of use in reinduction should be managed through the RSA as outlined in paragraph 7.14; and

- The EULAR guideline terminology of 'organ-threatening or life-threatening disease' be used as a treatment criteria in the restriction to align the eligible patient population with the intended definition of disease severity.

7.5 The PBAC considered that the nominated comparator GCs remained appropriate in the induction phase. In terms of maintenance, the PBAC recalled it had suggested a resubmission requesting treatment in the maintenance of remission should consider a comparison of avacopan with rituximab versus rituximab (para 7.6, avacopan PSD, July 2023 PBAC Meeting). The PBAC noted ESC advice that a robust comparison of avacopan and rituximab as maintenance therapies was not feasible between the ADVOCATE trial and the MAINRITSAN, MAINRITSAN 2, or RITAZAREM trials (see paragraph 6.34).

7.6 The ADVOCATE trial remained the key trial evidence in the resubmission. The primary efficacy outcomes of the ADVOCATE trial were disease remission (Week 26) and sustained remission (Week 52). The PBAC recalled that, while superiority in achieving disease remission was not demonstrated at Week 26, the Committee had considered avacopan may provide a benefit in terms of a strategy to reduce exposure to GCs over the induction period (see paragraphs 6.15 and 6.16). The PBAC also recalled avacopan + SOC was reported to be superior to prednisolone + SOC in achieving sustained remission at week 52, but the Committee had considered the comparison with no further treatment (following rituximab induction) was not consistent with current practice (para 7.10, avacopan PSD, July 2023 PBAC meeting).

7.7 The PBAC recalled the improvement in eGFR rates at both Week 26 and Week 52 evident for the population with renal disease. However, the PBAC had also noted that other parameters of renal disease such as urinary albumin:creatinine ratio (UCAR) at Week 52 and urinary MCP-1:creatinine ratio at Week 52 did not show any significant difference in patients with renal disease. The PBAC previously agreed with the ESC that the improvement in eGFR appeared to be driven by the eGFR < 30 ml/min/1.73m$^2$ subgroup and that it was not clear how much of the benefit was attributable to the group which compared avacopan to no maintenance therapy (para 7.11, avacopan PSD, July 2023 PBAC meeting). The PBAC noted the resubmission presented a post-hoc analysis of time to 40% reduction in UACR for participants with kidney involvement and a baseline UACR ≥10 mg/g to support the broader benefits of avacopan (see paragraphs 6.28 to 6.31). The PBAC noted from the sponsor hearing that renal physicians considered the potential early improvement in renal function was important for patients with eGFR in the low range who are at risk of organ failure. The PBAC noted the KDIGO (2024) guidelines stated that patients with lower GFR may benefit from greater glomerular filtration rate recovery (see paragraph 4.4).

7.8 Overall, the PBAC advised the claim of superior comparative effectiveness remained uncertain but was likely reasonable for induction therapy. The PBAC considered that such use would be consistent with the EULAR and KDIGO guidelines.

7.9 The PBAC advised that the clinical evidence provided did not adequately support a claim of superior comparative effectiveness for maintenance therapy. However, the PBAC considered that the use of avacopan for up to 12 months per treatment cycle would address a clinical need in this collection of relatively rare autoimmune diseases.

7.10 The PBAC reaffirmed its July 2023 advice that the claim of superior comparative safety was reasonable (para 6.39, avacopan PSD, July 2023 PBAC meeting).

7.11 The PBAC recalled that it had advised that a resubmission for avacopan should be based on the benefits of reducing GC when used as induction therapy (para 7.16, PSD, avacopan, July 2023 PBAC meeting). The resubmission argued that that avacopan provided statistically significant improvements in renal function (see paragraph 6.53) and retained the same economic model structure but revised a number of inputs in an attempt to address concerns raised in July 2023 (see paragraph 6.55). The PBAC acknowledged the ESC advice that while some changes to the economic model in the resubmission were more conservative, others were less so and a number of the concerns raised in July 2023 remained unaddressed. The PBAC noted that to address the issues raised by the ESC, the pre-PBAC response provided a revised base case that incorporated a rituximab maintenance weighting of 70%, a remission rate equal to GC + SOC values at 26 weeks, a utility decrement of 0.1 for any GC-related infections and treatment waning for avacopan after 3 months. The pre-PBAC response argued that it was appropriate to model a benefit in terms of eGFR based on data from the ADVOCATE trial and hence this approach was maintained in the revised base case. In addition, the pre-PBAC response offered a % price reduction from an EMP of $ to $. Noting the changes to the economic model and the price reduction offered in the pre-PBAC response, the PBAC considered the resulting incremental cost effectiveness ratio of $55,000 to < $75,000 /QALY high but acceptable given the clinical need.

7.12 The resubmission presented a revised financial model which applied a different approach to estimating the eligible population compared to the previous submission. The PBAC noted the use of revised incidence estimates based on data from the Queensland Hospital Admitted Patients Data Collection (QHAPDC) more than doubled the total patients treated. The PBAC agreed with the DUSC that the estimates presented in the resubmission were overestimated. The PBAC noted DUSC advice that the main reason for the substantial increase in estimates was because the resubmission had applied QHAPDC data to an incidence approach. The PBAC agreed with the DUSC that this approach was not appropriate. The PBAC noted the pre-PBAC response provided revised financial estimates that removed the 10% relapse rate and proposed a reduction in the uptake rates across the first 3 years of listing. The PBAC noted the approach taken to the use of QHAPDC data remained unchanged and did not accept the revised financial estimates presented in the pre-PBAC response.

7.13 The PBAC recalled the July 2023 submission had used an epidemiological approach with incidence estimates based on Australian data (Ormerod et al, 2008) with DUSC advising that the estimates were reasonable and aligned with the previous use of rituximab for the same indications (see paragraph 6.86). At that time the

epidemiological approach had identified four patient populations that would be eligible for avacopan: (1) newly diagnosed; (2) relapsed; (3) re-induction; (4) grandfathered patients. The PBAC recalled that it had advised the remaining uncertainty with respect to the eligible population could be reduced by removing Population 3 and grandfathered patients from the financial model (see paragraph 6.86). The PBAC did not accept the resubmission argument that a larger number of AAV patients were likely to be treated in Australia than anticipated in the July 2023 submission. The PBAC considered the incidence rate determined from QHAPDC data was inconsistent with the rates reported in a review of national and international data undertaken by Watts et al. 2015[10]. The Committee considered the results of the review suggested the use of the Ormerod et al. (2008) estimate remained appropriate. As such, the PBAC considered the July 2023 submission financial estimates would be reasonable with appropriate amendments. The amendments required to the July 2023 submission financial estimates included: the removal of Population 3 and grandfathered patients; changing the duration of treatment from 14.21 months to 9.6 months (the updated average treatment duration in the economic model); updating PBS co-payments for General and Concessional services; and incorporation of the revised price proposed in the pre-PBAC response.

7.14 The PBAC considered a Risk Sharing Arrangement would be required to address any residual uncertainty with the potential for use outside the proposed restriction, including leakage into use beyond 12 months as maintenance therapy or other settings where long-term data is not available and cost-effectiveness has not been demonstrated. The PBAC noted the pre-PBAC response proposed a % rebate for expenditure exceeding the financial estimates (see paragraph 6.97). The PBAC considered a % rebate appropriate and that the amended July 2023 financial estimates would form an appropriate basis for risk sharing arrangement subsidisation caps.

7.15 The PBAC advised that avacopan is not suitable for prescribing by nurse practitioners.

7.16 The PBAC recommended that the Early Supply Rule should not apply.

7.17 The PBAC recommended that avacopan should not be treated as interchangeable with any other drugs.

7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for avacopan:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over GCs, as while clinically relevant the treatment

[10] Watts RA, Mahr A, Mohammad AJ, et al. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis. Nephrol Dial Transplant. 2015 Apr:30 Suppl 1:i14-22. doi: 10.1093/ndt/gfv022.

benefit is likely to be modest;

b) The treatment is not expected to address a high and urgent unmet clinical need as GCs are available as an alternative. However, there is a clinical need for treatments that allow avoidance of high, cumulative GC use in this condition;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

# 8 Recommended listing

8.1 Add new item:

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| AVACOPAN | | | | | |
| avacopan 10 mg capsule, 180 | NEW 1 MP | 1 | 180 | 5 | Tavneos |
| | | | | | |
| | | | | | |
| **Restriction Summary [new 1] / Treatment of Concept: [new 1.1] Authority Required (telephone/online PBS Authorities system)** | | | | | |
| | **Category / Program:** GENERAL – General Schedule (Code GE) | | | | |
| | **Prescriber type: Prescriber type:** ☒Medical Practitioners | | | | |
| | **Restriction type:** ☒ Authority Required (telephone/online PBS Authorities system) | | | | |
| | **Indication:** Anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis | | | | |
| | | | | | |
| | **Treatment phase:** Induction treatment | | | | |
| | | | | | |
| | **Clinical criteria:** | | | | |
| | The condition must be severe granulomatosis with polyangiitis; or | | | | |
| | The condition must be severe microscopic polyangiitis | | | | |
| | **AND** | | | | |
| | **Clinical criteria:** | | | | |
| | The condition must be active at the time of the first prescription for this drug per treatment cycle. | | | | |
| | | | | | |
| | **Treatment criteria:** | | | | |
| | Patient must have ANCA associated vasculitis that is either (i) organ-threatening, (ii) life-threatening disease. | | | | |
| | 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. | | | | |
| | | | | | |
| | **AND** | | | | |
| | Patient must not receive more than 12 months of PBS subsidised treatment with this drug per induction | | | | |
| | | | | | |
| | **Prescribing Instruction:** | | | | |

| | |
|---|---|
| | A prescriber may apply for more than one induction treatment for their patient. |
| | |
| | **Administrative Advice:** |
| | Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 |

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

# 9 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.

# 10 Sponsor's Comment

CSL Seqirus welcomes the PBAC's recognition of the high unmet need for new treatments for severe AAV in Australia. We are committed to further data generation to illustrate the number of patients in Australia with severe AAV.