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CADTH Reimbursement Recommendation

Avacopan (Tavneos)

Indication: For the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard background therapy including glucocorticoids. Avacopan does not eliminate glucocorticoid use.

Sponsor: Otsuka Canada Pharmaceutical Inc.

Final recommendation: Do not reimburse

Summary

What Is the CADTH Reimbursement Recommendation for Tavneos?

CADTH recommends that Tavneos not be reimbursed by public drug plans as adjunctive treatment for adults with severe active antineutrophil cytoplasmic autoantibody-associated vasculitis (ANCA-AV) (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

Why Did CADTH Make This Recommendation?

- One clinical trial demonstrated that Tavneos in combination with ANCA-AV background therapy (including glucocorticoids and drugs that reduce immune system function) was as good as oral prednisone (60 mg dose reduced over 20 weeks) in combination with ANCA-AV background therapy for showing a reduction in disease symptoms at week 26 and was better than oral prednisone for maintaining symptom improvement at week 52. However, it was unclear if Tavneos offered a meaningful clinical benefit over other treatments used for ANCA-AV mainly because rituximab was not used as maintenance therapy in the trial, as is currently recommended by Canadian guidelines, and there is uncertainty around the clinical meaningfulness of the differences between the treatment groups for outcomes that assessed renal function, relapse, and Short Form [36] Health Survey version 2 (SF-36v2).
- There was not enough evidence to conclude that Tavneos met patients' needs for a treatment that reduces or eliminates the use of glucocorticoids and their side effects as well as improves their health-related quality of life (HRQoL).

Additional Information

What Is ANCA-AV?

ANCA-AV is a group of rare diseases that causes inflammation of small- and medium-sized veins and arteries and can often affect other organs in the body. It is expected that at least 80% of patients who do not receive treatment die within 1 year of diagnosis. With treatment, patients are still at a higher risk of serious infections and kidney failure due to worsening disease and/or because of treatment. The prevalence of ANCA-AV is estimated to be between 75 and 300 per million or approximately 1,700 to 2,500 total patients living in Canada.

Summary

Unmet Needs in ANCA-AV

Patients with ANCA-AV need effective treatments that reduce or eliminate the need for glucocorticoids and their side effects, prevent disease progression, and improve their HRQoL.

How Much Does Tavneos Cost?

Treatment with Tavneos is expected to cost approximately $75,000 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that avacopan not be reimbursed as adjunctive treatment for adults with severe active ANCA-AV (GPA and MPA) in combination with standard background therapy, including glucocorticoids (avacopan does not eliminate glucocorticoid use).

Rationale for the Recommendation

The ADVOCATE trial (N = 331) was a phase III, double-blind (DB), noninferiority, randomized controlled trial (RCT) in patients with ANCA-AV, which concluded that treatment with avacopan in combination with background therapy including glucocorticoids and immunosuppressants (IV or oral cyclophosphamide or IV rituximab) was noninferior to oral prednisone (60 mg tapered over 20 weeks) in combination with background therapy including glucocorticoids and immunosuppressants (IV or oral cyclophosphamide or IV rituximab) for achieving disease remission at week 26 and was superior for sustained disease remission at week 52. CDEC was unable to determine if avacopan fills an unmet therapeutic need, mainly because rituximab was not used as maintenance therapy in the ADVOCATE trial, and patients induced with IV rituximab did not receive any maintenance therapy, neither of which aligns with the current Canadian guidelines for the diagnosis and management of ANCA-AV. In addition, only the primary outcomes of disease remission at week 26 and sustained disease remission at week 52 were controlled for multiple testing; hence all other outcomes were at increased risk of type I error. Furthermore, the between-group differences for multiple secondary outcomes (week 4 Birmingham Vasculitis Activity Score [BVAS], urinary albumin/creatinine ratio [UACR], Vasculitis Damage Index [VDI], patients experiencing disease relapse, SF-36v2, and EQ-5D) were relatively small with wide confidence intervals (CIs). Therefore, the clinical and statistical significance of the differences between the treatment groups on these outcomes is unknown.

Patients expressed that they expect new treatments for ANCA-AV to be effective while reducing or eliminating the need for glucocorticoids and their associated side effects, and to improve HRQoL. Given that in the ADVOCATE trial, HRQoL measures were secondary end points not controlled for multiplicity, CDEC was unable to determine if avacopan had an impact on HRQoL. In addition, the impact of any differences in corticosteroid use did not indicate a meaningful difference in safety results between the treatment groups. CDEC concluded that available evidence for avacopan does not address these important unmet needs identified by the patients.

Discussion Points

- The sponsor requested a reconsideration of the initial CDEC draft recommendation to not reimburse avacopan for the adjunctive treatment of adults with severe active ANCA-AV (GPA and MPA) in combination with standard background therapy including glucocorticoids. CDEC discussed each of the issues identified by the sponsor in their Request for Reconsideration.

- During the initial and reconsideration meetings, CDEC acknowledged that rituximab as maintenance therapy for patients with ANCA-AV is not consistently reimbursed by all jurisdictions and, therefore, access to rituximab might not be equitable for all patients across Canada who are covered by a publicly funded drug plan. CDEC acknowledged that it would be ideal if all patients across Canada had equitable access to rituximab for ANCA-AV. However, CDEC discussed that rituximab was not used as maintenance therapy in the ADVOCATE trial, and patients induced with rituximab did not receive any maintenance therapy, neither of which aligns with the current Canadian guidelines for the diagnosis and management of ANCA-AV, which note that rituximab is 1 of the induction therapies and the first-line maintenance therapy after induction with cyclophosphamide or rituximab. This was due to rituximab not being approved as a maintenance therapy when the protocol for the ADVOCATE trial was being developed. Furthermore, it is unclear if the addition of avacopan to rituximab maintenance therapy would make a meaningful difference if these treatments were to be used in current clinical practice, as there is currently a lack of clinical data to inform this. CDEC also discussed that due to the lack of rituximab maintenance therapy, patients may have been undertreated, putting them at a higher risk of relapse and causing them to be less likely to achieve sustained remission. Thus, it is possible that the rates of relapse in the ADVOCATE trial do not accurately reflect expected outcomes with current clinical practice.
- CDEC discussed that for patients with renal disease at baseline, the least squares mean (LSM) difference in change from baseline between treatment groups for estimated glomerular filtration rate (eGFR) was 2.9 mL/min/1.73 m^2 (95% CI, 0.1 mL/min/1.73 m^2 to 5.8 mL/min/1.73 m^2) at week 26, 3.2 mL/min/1.73 m^2 (95% CI, 0.3 mL/min/1.73 m^2 to 6.1 mL/min/1.73 m^2) at week 52, and [redacted] at week 60, which appeared to be numerically in favour of avacopan treatment. CDEC noted that these changes were small throughout the trial, and it is uncertain whether the difference between treatment groups in eGFR levels is clinically meaningful. During the reconsideration meeting, CDEC noted that while patients with the most severe renal insufficiency possible may benefit the most in terms of improvement in eGFR levels (for patients with a baseline eGFR of less than 30 mL/min/1.73 m^2, the between-group LSM difference was 5.6 mL/min/1.73 m^2 [95% CI, 1.7 mL/min/1.73 m^2 to 9.5 mL/min/1.73 m^2] at week 52), and input from the clinical expert and clinician groups indicated that this change may be meaningful. However, statistical testing for renal function was not controlled for multiplicity, and the study was not powered to evaluate these subgroups based on severity; thus, conclusions cannot be drawn. In addition, a 52 week trial duration is also insufficient to evaluate the longer-term impacts of avacopan on renal function, and whether any improvement observed while on avacopan will be sustained when avacopan is discontinued after 52 weeks is unknown.
- During the initial and reconsideration meetings, CDEC discussed that the Glucocorticoid Toxicity Index (GTI) scores indicated fewer glucocorticoid-related toxicities for the avacopan group, which would be expected as this group received placebo prednisone instead of active prednisone tapered

during the first 20 weeks. However, Health Canada stated that the GTI was not validated for ANCA-AV and that "the end point was not specific enough to be discriminatory between treatment" groups.

- During the initial and reconsideration meetings, CDEC discussed that it was not possible to determine what effects were owing to avacopan given that the majority of participants received nonprotocol glucocorticoids. The use of nonstudy glucocorticoids for 89% of the trial's population and lack of data for the remaining 11% makes it difficult to assess avacopan versus prednisone without additional glucocorticoids. During the reconsideration meeting, CDEC noted that most patients used nonprotocol glucocorticoids and data for those who did not use glucocorticoids were unavailable. Nonstudy glucocorticoid use is problematic for quantifying the effect of avacopan treatment alone for both efficacy and harms outcomes; hence, it is uncertain if avacopan could induce and sustain remission without chronic glucocorticoid use at the levels currently used in standard of care (SOC) regimens.
- During the initial and reconsideration meetings, CDEC noted that dosing of corticosteroids could be performed in several ways and is more clinician-driven than protocol-driven; that is because there are numerous ways to dose and taper corticosteroids and it is generally based on clinical response, or a rebound in symptoms, rather than a set protocol; however, CDEC did recognize the necessity of the tapering protocol and relative congruence with practice.
- CDEC also discussed that the mean cumulative doses for any prednisone or its equivalent used in the trial were 1,348.9 mg (standard deviation [SD] = 2,040.3 mg) and 3,654.5 mg (SD = 1,709.8 mg) for the avacopan and prednisone groups, respectively, during the 52 week treatment period. Removing the protocol-tapered prednisone reduced the mean doses for just nonstudy prednisone or its equivalent to 1,348.9 mg (SD = 2,040.3 mg) and 1,265.3 mg (SD = 1,650.6 mg) for the avacopan and prednisone groups, respectively, during the treatment period. It is also unclear if these doses are high enough to effectively treat ANCA-AV or cause additional adverse effects.
- CDEC discussed that adverse events were generally balanced between treatment groups and that while treatment-emergent infections were higher in the prednisone group than the avacopan group (75.6% and 68.1%, respectively), the difference was not as large as would be expected in the ADVOCATE trial, where the aim was to eliminate glucocorticoids and the associated increased risk of infection. CDEC noted that this could be due to the short duration of oral prednisone used (60 mg tapered over 20 weeks) and the use of nonprotocol-specified glucocorticoids in both treatment groups.

Background

ANCA-AV is a group of rare, inflammatory disorders affecting mostly small- to medium-sized blood vessels, and includes GPA, MPA, and other vasculitides. ANCA-AV can vary from non–life-threatening to severe disease, where, in the latter, major organs are affected, and from limited (i.e., affecting a single organ) to systemic disease. Limited information exists in the literature about its incidence and prevalence in Canada. According to the clinical expert consulted by CADTH, the incidence of GPA and MPA together is estimated

to be 10 to 50 cases per million per year and prevalence is estimated to be between 75 and 300 cases per million or approximately 1,700 to 2,500 total patients living in Canada. Patients with ANCA-AV are at risk of increased morbidity and mortality largely due to the disease causing irreversible inflammatory organ damage and the consequences of long-term and often high-dose immunosuppressant drugs and glucocorticoids. It is expected that at least 80% of patients who go untreated will die within 1 year of diagnosis and even with treatment, patients are at increased risk of developing malignancies, serious infection, and end-stage kidney disease largely due to progressive disease and/or as a consequence of treatment.

According to the 2020 *Canadian Vasculitis Research Network (CanVasc) Consensus Recommendations for the Management of ANCA-AV*, IV methylprednisolone pulses are recommended for patients with life-threatening ANCA-AV followed by oral prednisone for those with severe disease. Patients with life-threatening disease are given cyclophosphamide or rituximab for a minimum of 3 to 6 months with glucocorticoids to induce remission. Cyclophosphamide and rituximab have shown similar efficacy for inducing remission; however, cyclophosphamide has been associated with fertility issues, alopecia, and malignancies, and rituximab may be preferred for specific patients (e.g., children, young adults concerned with infertility, and older adults with poor health). It is recommended that tapering glucocorticoids should begin within 2 weeks of induction therapy with cyclophosphamide or rituximab to reduce glucocorticoid exposure and their associated risks. Once remission is achieved, patients should be transitioned to maintenance therapy, preferentially rituximab (or azathioprine or methotrexate when rituximab maintenance cannot be used). It has been emphasized in the literature and by the clinical expert consulted by CADTH that maintenance treatment should continue for at least 2 years and additional treatment should be considered for those in high-risk groups (e.g., anti-proteinase 3 [PR3]-ANCA, prior relapse, pulmonary involvement, or upper respiratory tract involvement). Currently, the CanVasc recommendations state that the optimal duration for low-dose glucocorticoid use once remission is achieved is unknown.

Avacopan has been approved by Health Canada for the adjunctive treatment of adults with severe active ANCA-AV (GPA and MPA) in combination with standard background therapy including glucocorticoids and does not eliminate glucocorticoid use. Avacopan is a complement 5a receptor antagonist. It is available as 10 mg capsules and the dosage recommended in the product monograph is 30 mg (3 oral capsules of 10 mg each) taken orally twice daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, DB, noninferiority RCT in adults with ANCA-AV (GPA or MPA)
- patients' perspectives gathered by 1 patient group, Vasculitis Foundation Canada
- input from public drug plans that participated in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with ANCA-AV
- input from 1 clinician group, CanVasc

- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described in the following).

Stakeholder Perspectives

Patient Input

CADTH received 1 patient group submission from Vasculitis Foundation Canada, an organization that aims to increase disease awareness and research support for all forms of vasculitis. Vasculitis Foundation Canada invited its mailing list subscribers to complete an online survey and received input from 46 patients (35 with GPA and 11 with MPA) from Canada and the US who have experience using prednisone or avacopan. The patient group reported that GPA and MPA impact patients' daily lives and that patients experience a host of physical manifestations that lead to chronic fatigue, mood swings, poor sleep, chronic infections, and stress due to fear of relapse. Patients treated with prednisone reported side effects that significantly affect quality of life, including body disfiguration, steroid-induced diabetes or hypertension, infections requiring medical care, anxiety, and depression. Vasculitis Foundation Canada reported that patients with GPA or MPA indicated a need for a treatment that improves symptoms and quality of life that would also result in a reduction or elimination of the use of prednisone.

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH stated that patients need treatments that result in sustained remission, limited organ damage (or allow for better recovery from damage), limit the risk of severe infections, require less time on treatment (treatment shorter than 24 months has been associated with unacceptable high rates of relapse to date), and are safe for use in special populations (i.e., pediatric, pregnant, and older adult populations). The expert added that the disease and current ANCA-AV treatments have significant impact on patients' HRQoL and ability to work.

Per the clinical expert, avacopan would be used as a first-line treatment for adults with severe GPA or MPA in-line with the patient population for the ADVOCATE trial. Although patients with the most severe forms of disease were excluded from the trial, the expert suggested that these patients may also be candidates for the drug after the disease is controlled with high-dose glucocorticoids. In practice, the expert stated that avacopan would be administered to induce remission alongside IV or oral cyclophosphamide or IV rituximab with glucocorticoids. Once remission is achieved, the clinical expert noted that patients would usually receive appropriate maintenance therapy, such as rituximab at month 6 and every 6 months thereafter for at least 24 months of total treatment. There is currently a lack of clinical trial evidence for optimal patient management after 12 months of avacopan.

According to the expert, all adults with severe GPA or MPA could be treated with avacopan and it is not clear if there are any subpopulations who would respond better to the drug than other patients, given the available evidence.

The clinical expert noted that survival is the most important outcome. Other response measures include improvement of major organ disease (e.g., renal recovery, reduced use of mechanical ventilation), achieving remission (typically assessed at month 3, then month 6), and sustained remission (at months 12, 18, and 24 thereafter). The expert stated that it is also important to evaluate and limit the side effects caused by treatments. Although there are instruments to measure disease- and treatment-related changes in studies, the expert indicated that these are not used in routine clinical practice.

As was done in the ADVOCATE trial, the clinical expert stated that avacopan should be administered for 12 months and suggested that while the drug could be used for longer, there are limited data available for stopping the drug before 1 year or using it beyond that. According to the expert, discontinuing treatment should be considered if there are intolerable side effects, continual disease progression with clinical decline, or repeated relapses. Per the expert's opinion, another reason to discontinue avacopan is if it does not allow for a lesser use of glucocorticoids.

As GPA and MPA are rare diseases and require close monitoring, the clinical expert indicated that patients should be referred to a specialist with expertise in the disease area. In the clinical expert's opinion, a rheumatologist, nephrologist, general internal medicine specialist, respirologist, or intensive care unit doctor should be able to prescribe avacopan in a hospital setting, and it was noted that restricting the prescription to only rheumatologists or nephrologists with expertise in vasculitis would likely delay treatment initiation by many weeks. However, in community clinics, the expert believed it would be reasonable to restrict access to rheumatologists or nephologists with experience treating vasculitis.

The clinical expert emphasized that treatment with avacopan should be associated with a mandate to stop or significantly decrease glucocorticoids within the first weeks of initiating avacopan; otherwise, the continued use of avacopan should be clinically justified. Given the lack of long-term data, the expert expressed uncertainty in patient management after 12 months of avacopan and in the long-term outcomes after stopping the drug. Lastly, the clinical expert suggested that alongside the implementation of avacopan in Canada, it would be useful to set up a registry to track drug use and patterns of use, and to monitor safety and efficacy.

Clinician Group Input

CanVasc, a Canadian research network for vasculitis, provided input for this review. The clinician group expressed similar views to those of the clinical expert consulted by CADTH.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for avacopan:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy

- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- the generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The ADVOCATE trial (N = 331) was a phase III, DB RCT designed to investigate the efficacy and safety of avacopan in patients with ANCA-AV that aimed to determine if avacopan could induce and sustain remission without chronic glucocorticoid use at the levels currently used in SOC regimens. The trial compared avacopan (30 mg orally twice daily) to prednisone (60 mg per day orally tapered over 20 weeks) with respective matching placebos in addition to SOC therapy (IV or oral cyclophosphamide followed by azathioprine or IV rituximab without maintenance treatment) over 52 weeks with an 8-week follow-up. Patients were permitted to receive nonprotocol-specified low-dosage oral glucocorticoids (10 mg per day or less) for the treatment of adrenal insufficiency or allergic reaction. Eligible patients included adults who had a clinical diagnosis of GPA or MPA, were ANCA positive for either anti-PR3 or antimyeloperoxidase antibodies, and had active disease at screening. Patients with limited or most severe disease (alveolar hemorrhage requiring mechanical ventilation or with an eGFR of less than 15 mL/min/1.73 m^2 at baseline) were not eligible. The primary outcomes were the proportions of patients who achieved disease remission at week 26 and sustained disease remission at week 52. Key secondary outcomes included GTI, HRQoL (SF-36v2, 5-Level EQ-5D [EQ-5D-5L], and EQ Visual Analogue Scale [VAS]), the proportion of patients experiencing disease relapse, kidney function (eGFR, UACR), and systemic damage (VDI). Harms and notable harms identified in the CADTH systematic review protocol were also assessed.

At baseline, the mean age of patients was 60.9 years (SD = 14.5 years), more than half were male (56.5%), and most were white (84.3%). Most patients were newly diagnosed with ANCA-AV (69.4%) compared to having relapsing disease (30.6%), more than half of patients had GPA (54.8%) compared to MPA (45.2%), and less than half were positive for anti-PR3 antibodies (43.0%) compared to antimyeloperoxidase antibodies (57.0%).

Efficacy Results

Survival was not assessed as an efficacy outcome in the trial but was captured as deaths for harms outcomes. Hospitalizations were not assessed in the trial. Symptoms (e.g., fatigue) were not assessed as an efficacy outcome but some symptoms may have been captured as harms outcomes. Only the primary

outcomes of disease remission at week 26 and sustained disease remission at week 52 were controlled for multiple testing.

Disease Remission (Induction and Sustained Remission)

Based on the intention-to-treat analyses, 72.3% (95% CI, 64.8% to 78.9%) of patients randomized to avacopan and 70.1% (95% CI, 62.5% to 77.0%) of patients randomized to prednisone achieved remission at week 26. The estimate of common difference in remission rates between groups was 3.4% (95% CI, −6.0% to 12.8%; noninferiority $P < 0.0001$ and superiority $P = 0.2387$). Findings for the per-protocol population were similar.

At week 52, 65.7% (95% CI, 57.9% to 72.8%) of patients randomized to avacopan and 54.9% (95% CI, 46.9% to 62.6%) of patients randomized to prednisone achieved sustained remission. The estimate of common difference in sustained remission rates between groups was 12.5% (95% CI, 2.6% to 22.3%; noninferiority $P < 0.0001$ and superiority $P = 0.0066$). Findings for the per-protocol population were similar.

Renal Function (e.g., eGFR, Progression to End-Stage Kidney Disease)

For patients with renal disease at baseline (based on the BVAS renal component), the LSM difference in change from baseline between treatment groups for eGFR was 2.9 mL/min/1.73 m^2 (95% CI, 0.1 mL/min/1.73 m^2 to 5.8 mL/min/1.73 m^2) at week 26, 3.2 mL/min/1.73 m^2 (95% CI, 0.3 mL/min/1.73 m^2 to 6.1 mL/min/1.73 m^2) at week 52, and [redacted] at week 60. In total, 7 patients required dialysis during the trial: 3 patients (1.8%) in the avacopan group and 4 patients (2.4%) in the prednisone group.

For patients with renal disease (based on the BVAS renal component) and albuminuria (defined as a UACR of at least 10 mg/g creatinine) at baseline, the LSM difference between groups in change from baseline for UACR was 1.3 mg/g (95% CI, 1.0 mg/g to 1.6 mg/g) at week 26, 1.1 mg/g (95% CI, 0.9 mg/g to 1.5 mg/g) at week 52, and [redacted] at week 60.

Systemic Damage (e.g., as Measured by VDI)

Based on the data assessed by the adjudication committee, the LSM difference in change from baseline between treatment groups for the VDI was 0.1 (95% CI, −0.1 to 0.3) at week 26, 0.0 (95% CI, −0.2 to 0.3) at week 52, and [redacted] at week 60.

Disease Relapse (e.g., Time to Relapse or Duration of Remission, Minor Versus Major)

For patients who achieved remission at week 26 (n = 120 in the avacopan group and n = 115 in the prednisone group), [redacted] of patients in the avacopan group and [redacted] of patients in the prednisone group experienced disease relapse. The estimate of common difference in rates was [redacted]. The hazard ratio was 0.46 (95% CI, 0.25 to 0.84) for avacopan versus prednisone. Due to the small number of patients who relapsed, the median time to relapse was not estimable and Kaplan-Meier estimates were not calculated. During the 8-week follow-up period, 3.8% of patients in the avacopan group and 4.5% of patients in the prednisone group experienced disease relapse.

Glucocorticoid Use and Related Toxicities and Safety

The LSM difference between treatment groups for the GTI Cumulative Worsening Score was −11.0 (95% CI, −19.7 to −2.2) at week 13 and −16.8 (95% CI, −25.6 to −8.0) at week 26. The LSM difference between treatment groups for the GTI Aggregate Improvement Score was −13.3 (95% CI, −22.2 to −4.4) at week 13 and −12.1 (95% CI, −21.1 to −3.2) at week 26.

Health-Related Quality of Life

The LSM difference in change from baseline between treatment groups for the SF-36v2 Mental Component Summary was 1.6 (95% CI, −0.6 to 3.8) at week 26, 1.7 (95% CI, −0.5 to 3.9) at week 52, and [redacted] at week 60. The LSM difference between treatment groups for the SF-36v2 Physical Component Summary was 3.1 (95% CI, 1.2 to 5.0) at week 26, 2.4 (95% CI, 0.4 to 4.3) at week 52, and [redacted] at week 60.

The LSM difference in change from baseline between treatment groups for the EQ-5D VAS was 3.6 (95% CI, −0.1 to 7.2) at week 26, 5.9 (95% CI, 2.3 to 9.6) at week 52, and [redacted] at week 60. The LSM difference between treatment groups for the EQ-5D-5L index score was 0.0 (95% CI, 0.0 to 0.1) at week 26, 0.1 (95% CI, 0.0 to 0.1) at week 52, and [redacted] at week 60.

Harms Results

Nearly all patients in the avacopan (98.8%) and prednisone (98.2%) groups experienced at least 1 treatment-emergent adverse event (TEAE). The 3 most common TEAEs in the avacopan group were nausea (23.5% with avacopan versus 20.7% with prednisone), peripheral edema (21.1% with avacopan versus 24.4% with prednisone), and headache (20.5% with avacopan versus 14.0% with prednisone). The 3 most common TEAEs in the prednisone group were peripheral edema, arthralgia (22.0% with prednisone versus 18.7% with avacopan), and muscle spasms (22.6% with prednisone versus 10.8% with avacopan).

Overall, 42.2% of patients in the avacopan group and 45.1% of patients in the prednisone group experienced a serious adverse event. The most common serious adverse events were ANCA-positive vasculitis (7.2% with avacopan versus 12.2% with prednisone) and pneumonia (5.4% with avacopan versus 5.5% with prednisone).

In total, 16.3% of patients in the avacopan group and 17.1% of patients in the prednisone group stopped treatment due to adverse events. The most common reason was ANCA-positive vasculitis (2.4% with avacopan versus 4.9% with prednisone) and other reasons occurred at a frequency of less than 2% for either group.

Six patients died during the treatment period in the ADVOCATE trial (2 patients receiving avacopan versus 4 patients receiving prednisone).

Notable Harms

Treatment-emergent infections were reported among 68.1% and 75.6% of patients in the avacopan and prednisone groups, respectively. Serious treatment-emergent infections were reported among 13.3% and 15.2% of patients in the avacopan and prednisone groups, respectively, of which pneumonia was the most common serious infection–related TEAE (4.8% and 3.7%, respectively). Infections resulted in 9 patients withdrawing from the trial and 3 deaths.

Elevated alanine aminotransferase was reported by 4% and 2% of patients in the avacopan and prednisone groups, respectively; elevated aspartate aminotransferase was reported in 2% and 0% of patients in the respective groups; and elevated blood bilirubin was reported in 2% of patients in the avacopan group and 1% of patients in the prednisone group.

Acute myocardial infarction was reported by 1.2% of patients in the prednisone group and 0.6% of patients in the avacopan group, while cardiac failure was reported by 1.2% of patients in the avacopan group (and none in the prednisone group). Cardiac vasculitis was not reported in the trial.

Nausea was reported by 23.5% and 20.7% of patients in the avacopan and prednisone groups, respectively; diarrhea was reported by 15.1% and 14.6% of patients in the respective groups; vomiting was reported by 15.1% and 12.8% of patients, respectively; and dyspepsia was reported by 3.0% and 6.1% of patients, respectively.

Angioedema was reported by 1.2% of patients in the avacopan group (and none in the prednisone group).

Critical Appraisal

The first notable limitation with the ADVOCATE trial was that rituximab was not used as maintenance therapy and patients induced with rituximab did not receive any maintenance therapy, neither of which aligns with the current Canadian guidelines for the diagnosis and management of ANCA-AV, which recommend using rituximab as first-line SOC maintenance therapy. This was due to rituximab not being approved as a maintenance therapy when the protocol for the ADVOCATE trial was being developed. Furthermore, it is unclear if the addition of avacopan to rituximab maintenance therapy would make a meaningful difference if these treatments were to be used in clinical practice today and there is currently a lack of clinical data to inform this. The second major limitation was the trial's use of nonstudy immunosuppressants (19.7%) and glucocorticoids (89.1%). Nonstudy medication use is problematic for quantifying the effect of avacopan treatment alone for both efficacy and harms outcomes, and data for those who did not use glucocorticoids were unavailable. The Health Canada indication has specified avacopan as an add-on or adjunctive therapy to standard treatment rather than a glucocorticoid-sparing drug. These deviations from currently recommended SOC maintenance therapy and from the protocol likely biased the results, though the magnitude and direction of the bias are unknown. Other issues included the relatively large number of discontinuations from treatment (more than 20% in either group), which resulted in missing data for nearly all outcomes; multiple outcome measures not being validated for ANCA-AV; and the absence of published minimal important differences for this population.

Patients with ANCA-AV who have only ever had negative antibody results as well as those with very severe disease were excluded from the ADVOCATE trial and it is uncertain if the results of the trial can be generalized to patients with these characteristics. Also, the apparent difference in glucocorticoid use between treatment groups is more likely attributable to the trial design rather than a change in disease activity; for example, if avacopan was effectively controlling ANCA-AV. The instruments used in the ADVOCATE trial are not used in clinical practice, secondary outcomes were not controlled for multiplicity, and between-group differences for multiple secondary outcomes (week 4 BVAS, UACR, VDI, patients experiencing

disease relapse, SF-36v2, and EQ-5D) were relatively small with wide CIs. Lastly, there was no rationale for the trial duration being 52 weeks or the follow-up being 8 weeks, and it is uncertain what long-term (beneficial or harmful) effects there are after discontinuing avacopan treatment. There was no indication from the trial about what posttreatment strategies should be used to manage patients with ANCA-AV and there is a lack of data informing this or whether avacopan can be continued for longer than 12 months.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with severe ANCA-AV (GPA and MPA)
Treatment	Avacopan in combination with SOC (rituximab or cyclophosphamide)[a]
Dose regimen	30 mg (3 x 10 mg capsules) orally twice daily
Submitted price	Avacopan, 10 mg: $34.24 per capsule
Treatment cost	Annual cost of $75,051
Comparators	• Rituximab and glucocorticoids • Cyclophosphamide and glucocorticoids
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime
Key data source	• ADVOCATE trial designed to compare an avacopan-based regimen vs. GC-based SOC regimens in patients with ANCA-AV • Equal rates of remission for rituximab and cyclophosphamide were assumed based on noninferiority of rituximab in the RAVE clinical trial
Key limitations	• The risk of ESRD is highly uncertain, as it was informed by eGFR improvement from a single measure in the ADVOCATE trial and suggests a significant reduction in the risk of ESRD associated with eGFR. Using a single eGFR measure is problematic as eGFR value can change daily, and expert opinion indicated that eGFR changes in the trial were highly unlikely to achieve the predicted risk reduction. This likely overestimates both the magnitude of the estimated QALY gain and the ESRD costs savings associated with avacopan. • The sponsor's use of azathioprine as the first-line maintenance therapy for all patient who achieved remission is not reflective of current clinical practice. Both CanVasc guidelines and the clinical expert consulted by CADTH for the review recommended rituximab, due to its higher success rate in reducing major relapses. The use of azathioprine as a maintenance therapy likely inflates the risk of relapse and associated costs, thus biasing the results in favour of avacopan plus SOC. • The sponsor assumed avacopan treatment for 1 year. However, according to clinical expert feedback, avacopan is anticipated to be used for reinduction therapy and for a period of 2 years when initiated,

Component	Description
	which was not modelled. • In the ADVOCATE trial, nearly all patients had exposure to nonstudy-supplied GCs. Given the nonstudy medication use, it is difficult to quantify the efficacy of avacopan, specifically what benefit is attributed to avacopan vs. GCs use. The clinical expert consulted by CADTH for this review noted that the uncontrolled use of GCs in the trial likely biased the effect estimates.
CADTH reanalysis results	• CADTH conducted reanalyses to address some of the key limitations, which included considering a pooled hazard ratio for ESRD per change in eGFR, selecting rituximab as the first-line maintenance therapy, assuming the use of avacopan for reinduction treatment, assuming a 2-year treatment duration for avacopan, and applying the same utility value for the transplant and remission health states. • In CADTH's base case, the ICER for avacopan plus SOC compared to SOC alone is $365,453 per QALY gained (incremental costs = $154,511; incremental QALYs = 0.423) in adults with severe ANCA-AV. A price reduction of 72.5% would be needed for avacopan plus SOC to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

ANCA-AV = antineutrophil cytoplasmic autoantibody-associated vasculitis; CanVasc = Canadian Vasculitis Research Network; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GC = glucocorticoids; GPA = granulomatosis with polyangiitis, ICER = incremental cost-effectiveness ratio; LY = life-year; MPA = microscopic polyangiitis, QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

[a]There was an uncontrolled use of nonstudy GCs with a mean dosage of 4 mg per day per patient.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor may have inaccurately estimated the total population eligible for treatment with avacopan, the uptake of avacopan plus SOC is expected to be higher than that estimated by the sponsor, and the rate of adherence for GCs is expected to be lower than that estimated by the sponsor.

CADTH reanalyses increased the proportion of incident patients treated with avacopan, decreased the proportion of prevalent patients treated with avacopan, changed the market share of avacopan, and decreased the rate of adherence for GCs. Based on the CADTH reanalyses, the estimated budget impact from reimbursing avacopan is expected be $4,099,173 in year 1, $8,319,444 in year 2, and $10,130,799 in year 3, for a 3-year total budget impact of $22,549,415.

Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for avacopan for the adjunctive treatment of adults with severe active ANCA-AV (GPA and MPA) in combination with standard background therapy including glucocorticoids. In their request, the sponsor identified the following issues:

- According to the sponsor, rituximab is not publicly reimbursed for maintenance therapy in most provinces, and is therefore not an SOC for maintenance therapy in ANCA-AV among the majority of participating public drug plans in Canada.
- According to the sponsor, despite the absence of rituximab as maintenance therapy in the RCT, remission achieved with rituximab induction was maintained by avacopan in monotherapy and showed superiority versus prednisone at 52 weeks.

- According to the sponsor, the ADVOCATE trial achieved both primary end points of noninferiority for remission at week 26 and superiority for sustained remission at week 52 (BVAS = 0) without receiving any GCs within the 4 weeks before evaluation at weeks 26 and 52, demonstrating the effect of avacopan treatment without concomitant GCs. Furthermore, GC use was reasonably well balanced between the 2 study groups.
- According to the sponsor, the protocolized tapering of the prednisone dosage is widely followed in clinical practice, as per the CanVasc recommendations.
- According to the sponsor, the instruments used in the trial (e.g., BVAS, VDI, SF-36v2) are validated, along with UACR and relapse, and are informing clinicians on the important outcomes for patients with ANCA-AV. Furthermore, these instruments have a precedent for acceptability by regulatory agencies and have been used for years in previous clinical trials in ANCA-AV.
- According to the sponsor, avacopan demonstrated statistically significant improvements in SF-36 for all of the physical domains and the vitality component of the mental health domain compared to the prednisone group. It also showed significantly larger improvement in EQ-5D VAS score from baseline in the avacopan group, as well as for the EQ-5D-5L health scale index score.
- According to the sponsor, avacopan demonstrated a clinically meaningful improvement in eGFR versus prednisone over the course of the 52-week treatment period. The improvement was more than 4 times greater than a minimal clinically meaningful improvement in patients with severe kidney involvement and nearly 10 times greater than a minimal clinically meaningful improvement in those with very severe kidney involvement.

In the meeting to discuss the sponsor's Request for Reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in the diagnosis and management of patients with ANCA-AV
- feedback from the public drug plans
- feedback from 6 clinician groups: physicians caring for vasculitis in Calgary, Drs. Bryce Barr and David Robinson Vasculitis Clinic, the Renal Pharmacists' Network, CanVasc, Waterloo Rheumatology, and Scarborough Regional Health Nephrologists
- feedback from 1 patient group: Vasculitis Foundation Canada.

All stakeholder feedback received in response to the draft recommendation from clinician groups and the public drug programs is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial meeting date: March 24, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration meeting date: July 27, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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