CADTH

CADTH REIMBURSEMENT REVIEW

# Stakeholder Feedback on Draft Recommendation

**avacopan (Tavneos)**

(Otsuka Canada Pharmaceutical Inc.)

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

**April 27, 2023**

April 21, 2023

To: The Canadian Agency for Drugs and Technologies in Health

**Subject: Feedback regarding the CADTH draft recommendation to not reimburse avacopan for the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)- associated vasculitis**

This letter, on behalf of the Canadian Vasculitis research network (CanVasc) summarizes CanVasc's current position on the use of avacopan for the treatment of ANCA-associated vasculitis (AAV) and calls for reconsideration of the decision to not reimburse avacopan in Canada.

***ANCA-associated vasculitis*** is a severe systemic disease commonly involving the kidneys and lungs ***with >80% mortality if untreated, and a significant rate of major organ damage, including end-stage renal disease despite treatment***. The currently recommended induction treatment for severe disease is glucocorticoids combined with cyclophosphamide or rituximab. However, mortality remains elevated in AAV with the ***main cause of death being infections*** driven by both disease and treatment-related risks. Additionally, ***chronic kidney disease is common and associated with worse outcomes. Glucocorticoid-associated adverse events (e.g., diabetes, obesity, osteoporosis, and psychiatric complications) further contribute to increased cardiovascular risk and impact quality of life***. Therefore, reducing glucocorticoid exposure is an important principle for the management of AAV and several strategies have been investigated, including the adjunctive use of avacopan. The latter is the only agent to date to have shown a substantial reduction in the use of glucocorticoids, without decreasing the rate of sustained remission. Data suggests greater sustained remission rates and better renal recovery when using avacopan.

***Hence, CanVasc, like other international vasculitis groups, identified the importance of avacopan in the current therapeutic strategy for GPA and MPA, and recently published recommendations to provide guidance for the use of avacopan in AAV*** (Turgeon et al. Rheumatology 2023)***.*** CanVasc, established in 2010 by Drs. Carette, Pagnoux (University of Toronto) and Dr. Khalidi (McMaster University) is a not-for-profit organization consisting of representatives from clinical and research centers across Canada with an expertise in vasculitis.

CanVasc published the first North American recommendations for the management of ANCA-associated vasculitis (McGeoch et al. J Rheumatol 2016) with an update in 2020 (Mandel et al. J Rheumatol 2020). In 2023, an addendum on avacopan was developed by >30 physicians (adult and pediatric rheumatologists, nephrologists and general internists) with expertise in AAV. This was the first published recommendations on avacopan in the world. Since then, the European Alliance of Associations for Rheumatology (EULAR) group also published a recommendation on avacopan for the management of ANCA-associated vasculitis (Hellmich et al. Ann Rheum Dis 2023), while the drug is being incrementally approved in several countries in Europe for reimbursement (France, UK).

***Based on the available evidence (3 randomized controlled trials and 2 observational studies), three recommendations for the use of avacaopan in AAV were made by the CanVasc group, with a high level of agreement among the working group (>90%).***

The three recommendations are as follows:

1. ***The addition of oral avacopan (30 mg twice daily) can be considered for induction of remission in patients with newly diagnosed or relapsing GPA or MPA treated with cyclophosphamide or rituximab***

We also emphasized that "certain populations may especially benefit from avacopan, such as those at high risk of glucocorticoid toxicity (pre-existing diabetes, metabolic syndrome, cardiovascular disease, osteoporosis, glaucoma, cataracts, neuropsychiatric disorders, susceptibility to recurrent or severe, infections) or those with renal or refractory disease. Additional studies are needed to determine if certain patients have superior benefit from the use of avacopan."

2. ***After starting avacopan, a faster glucocorticoid tapering protocol aiming for discontinuation by the end of week 4 should be considered***

In the ADVOCATE trial, the cumulative dose of glucocorticoids in the avacopan arm was substantially lower than in the control group, which received a currently standard 5-month regimen of glucocorticoid. Also, 12% of patients in the avacopan group did not receive any glucocorticoids after trial initiation. The reduction in glucocorticoid exposure resulted in less glucocorticoid-related adverse events, but this was not the primary endpoint of the study and was thereby possibly underpowered to detect a larger safety signal. Given that ADVOCATE required tapering off all pre-trial glucocorticoids within 4 weeks, CanVasc recommended this fast taper with close monitoring for relapses to maximize steroid-sparing effects. We acknowledge that a rapid glucocorticoid taper in conjunction with avacopan may not be appropriate for all patients and should be used with clinical judgement (noting that patients with very severe disease were excluded from the trial).

3. ***When initiated as part of induction therapy, avacopan can be continued for one year***

The ADVOCATE trail continued avacopan therapy for 1 year with outcomes reported at 6 and 12 months. Treatment duration of avacopan was 3 months in the CLEAR and CLASSIC trials. Therefore, CanVasc recommended up to 12 months treatment with avacopan, as done in ADVOCATE and acknowledge the need for more studies and/or registry to determine the optimal duration of avacopan use, and its combination with other agents such as rituximab for maintenance of remission.

Avacopan as adjunctive therapy for adults with severe AAV (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapies has been approved by Health Canada, the FDA in the USA and agencies in Europe. For this approved use, avacopan is now being prescribed globally.

The benefit of avacopan for renal function has also been found of interest, whereas the place of plasma exchange remains debated- its benefit is more limited than shown with avacopan in the ADVOCATE study, and carries a higher risk of infection, that avacopan does not.

Hence, CanVasc feels that based on the available evidence and current positions of numerous other international expert groups and reimbursement institutions, there is a role for avacopan in the treatment of patients with severe GPA or MPA. There is no alternative or equivalent agent available to date in Canada that would achieve such a substantial steroid-sparing effect and may additionally help maintain remission and improve renal outcomes. Patients are now aware of this agent, its expected benefit and current use abroad. CanVasc is concerned that the CADTH recommendation to not reimburse avacopan will disproportionately affect access to this drug in Canada for low income and marginalized populations. The limitation in the use of avacopan in Canada will also impact research on this agent, while registries have been initiated now in Europe and USA where access to drug has been approved.

Sincerely,

[redacted]

Lillian Barra, MD MPH
CanVasc President
Western University
St. Joseph's Health Care London
268 Grosvenor St. D2-160
London, Ontario N6A 4V2
[redacted]

[redacted]

Christian Pagnoux, MD, MSc, MPH
CanVasc Vice-President and Founder
Vasculitis clinic, Mount Sinai Hospital
Toronto, Ontario
[redacted]

[redacted]

Nader Khalidi, MD, FRCPC
CanVasc Member and Co-Founder
Professor of Medicine, McMaster University
St. Joseph's Hospital
50 Charlton Ave East Fontbonne F336
Hamilton, ON L8N 4A6
[redacted]

[redacted]

Stephanie Garner, MD MSc
CanVasc Treasurer
University of Calgary
South Health Campus
4448 Front St. SE
Calgary, Alberta T3M 1M4
[redacted]

***References:***


1. *Hellmich B et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2023 Mar 16:ard-2022-223764. doi: 10.1136/ard-2022-223764. Epub ahead of print. PMID: 36927642.*

2. *Jayne DRW et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. J Am Soc Nephrol. 2017 Sep;28(9):2756-2767. doi: 10.1681/ASN.2016111179. Epub 2017 Apr 11. PMID: 28400446; PMCID: PMC5576933.*

3. *Jayne DRW. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med. 2021 Feb 18;384(7):599-609. doi: 10.1056/NEJMoa2023386. PMID: 33596356.*

4. *McGeoch L et al. Canadian Vasculitis Research Network. CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides. J Rheumatol. 2016 Jan;43(1):97-120. doi: 10.3899/jrheum.150376. Epub 2015 Nov 1. PMID: 26523024.*

5. *Merkel PA et al. Adjunctive Treatment With Avacopan, an Oral C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. ACR Open Rheumatol. 2020 Nov;2(11):662-671. doi: 10.1002/acr2.11185. Epub 2020 Oct 31. PMID: 33128347; PMCID: PMC7672305.*

6. *Turgeon D et al. CanVasc consensus recommendations for the use of avacopan in antineutrophil cytoplasm antibody-associated vasculitis: 2022 addendum. Rheumatology (Oxford). 2023 Feb 21:kead087. doi: 10.1093/rheumatology/kead087. Epub ahead of print. PMID: 36805625.*

CADTH

# CADTH Reimbursement Review

# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0732-000 |
| Brand name (generic) | Avacopan |
| Indication(s) | Antineutrophil cytoplasmic antibody-associated vasculitis |
| Organization | Physicians caring for vasculitis in Calgary |
| Contact information[a] | Name: Stephanie Garner |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | ☒ |

ANCA associated vasculitis is a complex multisystem disease that requires collaborative care delivered in a centre with vasculitis expertise (1). While advances in therapy have led to improved mortality, infections, and cardiovascular disease (CVD) are the leading cause of death in this population (2, 3). The cumulative dose of steroids has been shown to contribute not only to infection risk, but other adverse effects including diabetes, osteoporosis, impaired health related quality of life and accrued organ damage (4-8). In vasculitis, we know that for every 1000 mg of prednisone exposure, there is a 3% increase in adverse events (9). Even 5 mg of prednisone or less has been associated with an increase in all cause CVD risk (HR 1.74) in patients with rheumatic disease (10). Having steroid sparing tools in our armamentarium for a disease that has a five-year mortality of up to 22% is critical (11).

Avacopan is the first new therapeutic in AAV since rituximab was introduced in 2010 (12). There have been three randomized controlled clinical trials which have demonstrated that when used as adjuvant therapy it is safe, results in less steroid exposure and improves renal outcomes (13-15).

In response to a few of the specific discussion points raised by CADTH on page 4:

***Rituximab was not used as maintenance therapy***

The use of rituximab as maintenance therapy is not the standard of care across Canada and does not reflect the Canadian guidelines for the management of AAV (1). Rituximab is also not publicly funded for maintenance therapy in Alberta.

***Change in eGFR from baseline was not clinically meaningful***

In a subgroup analysis of patients in ADVOCATE trial who presented with an eGFR ≤ 20/min, the patients in the avacopan group had a 16.1 ml/min per 1.73m$^2$ improvement versus the placebo group, which only had a 7.7 ml/min per 1.73m$^2$ improvement(16). As well, in this subgroup analysis, the risk of adverse events in the avacopan group was only 48%, while it was 70% in the prednisone group. In our opinion, this is an extremely meaningful difference, as those patients with severe renal involvement have a much higher risk of kidney failure and major adverse cardiac events.

***Glucocorticoid Use***

While the reviewers raised concerns about non-protocol steroid use, the placebo arm was exposed to a mean of over two grams more of prednisone than those in the avacopan arm. Given the known long-term risks of prednisone exposure described above we feel this is very clinically relevant.

We would also respectfully disagree that protocolized steroid tapering is not clinical practice. Since the PEXIVAS clinical trial was published in 2020, the used of the published reduced dose steroid tapering schedule has been widely accepted and used at vasculitis centres across Canada (17).

We feel strongly that CADTH should recommend the reimbursement of avacopan in Canada. To not do so would adversely affect access to a safe and effective therapy for many Albertans who do not have private drug coverage.

| **Expert committee consideration of the stakeholder input** | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
| | No | ☒ |
| The patient foundation and the clinician who participated in the review both stated it should be available (Pages 5 and 6) | | |

| **Clarity of the draft recommendation** | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☒ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☒ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☐ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |

[a] CADTH may contact th s person f comments requ re c ar f cat on.

## Appendix 2. Conflict of Interest Declarations for Clinician Groups

| A. Assistance with Providing the Feedback | | |
|---|---|---|
| **1. Did you receive help from outside your clinician group to complete this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |

| B. Previously Disclosed Conflict of Interest | | |
|---|---|---|
| **3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.** | No | ☐ |
| | Yes | ☐ |
| • *We did not submit for the initial application. This is our first submission.* | | |

### C. New or Updated Conflict of Interest Declarations

| New or Updated Declaration for Clinician 1 | |
|---|---|
| **Name** | *Aurore Fifi-Mah* |
| **Position** | *Clinical associate professor* |
| **Date** | *28-April-2023* |
| x | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Otsuka* | x | ☐ | ☐ | ☐ |
| *Sanofi* | | x | ☐ | ☐ |
| *Organon* | x | | | |
| *Johnson-Johnson* | x | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 2 | |
|---|---|
| **Name** | *Stephanie Garner* |
| **Position** | *Clinical Assistant Professor* |
| **Date** | *28-4-2023* |

| | |
|---|---|
| ☒ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Otsuka* | ☒ | ☐ | ☐ | ☐ |
| *UCB* | ☐ | ☒ | ☐ | ☐ |
| *AbbVIe* | ☒ | ☐ | ☐ | ☐ |
| *Novartis* | ☒ | ☐ | ☐ | ☐ |
| *Janssen* | ☒ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 3** | |
|---|---|
| **Name** | *Dr. Kim Cheema* |
| **Position** | *Clinical Assistant Professor* |
| **Date** | *28-4-2023* |
| ☒ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Novartis* | ☒ | ☐ | ☐ | ☐ |
| *Alexion* | ☒ | ☐ | ☐ | ☐ |
| *GSK* | ☒ | ☐ | ☐ | ☐ |
| *AB002 Drug and Safety Monitoring Board* | ☒ | ☐ | ☐ | ☐ |

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10. Pujades-Rodriguez M, Morgan AW, Cubbon RM, Wu J. Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. PLoS Med. 2020;17(12):e1003432. Epub 20201203. doi: 10.1371/journal.pmed.1003432. PubMed PMID: 33270649; PubMed Central PMCID: PMC7714202.

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15. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med. 2021;384(7):599-609. doi: 10.1056/NEJMoa2023386. PubMed PMID: 33596356.

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# CADTH Reimbursement Review
# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR)732-000 |
| Brand name (generic) | Tavenos |
| Indication(s) | ANCA associated Vasculitis |
| Organization | Renal Pharmacists' Network |
| Contact information[a] | Name:Jenny Ng [redacted] |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | ☒ |
| Yes, many points are valid in the critical analysis of the ADVOCATE study. | | |

| Expert committee consideration of the stakeholder input | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
| | No | ☒ |
| Recommendations do not take into consideration patients who are at high risk of steroid SE (such as pts with previous fracture, diabetes, mood disorders etc) /previously have not tolerated steroid therapy who may require alternative therapy option. | | |

| Clarity of the draft recommendation | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☒ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☒ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☒ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |

[a] CADTH may contact this person if comments require clarification.

| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
|---|---|---|---|---|
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Otsuka * manufacturer of Avacopan* | ☒ | ☐ | ☐ | ☐ |
| *Have received other manufacturer sponsorship but they are not directly associated with Avacopan* | ☒ | | | |

| **New or Updated Declaration for Clinician 2** | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
|---|---|---|---|---|
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 3** | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☒ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
|---|---|---|---|---|
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

# CADTH Reimbursement Review
# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0732-000 |
| Brand name (generic) | Tavneos (Avacopan) |
| Indication(s) | Antineutrophil cytoplasmic antibody-associated vasculitis |
| Organization | Scarborough Regional Health - Nephrologists |
| Contact informationa | Dr. Robert Ting, Nephrologist, Scarborough Regional Health |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | ☒ |

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

One of the conclusions by CADTH was that the differences in change from baseline between different treatment groups was small throughout the trial.

ANCA associated vasculitis often involves the kidneys with up to one third of patients developing renal failure, however the attack on the kidneys is not consistent in all cases of ANCA vasculitis. Even if one considers the overall population population with renal involvement, the benefit of Avacopan over Prednisone was 3.2 ml/min/year which is actually more than we see with use of Tolvaptan in ADPKD or with SGLT2 inhibitors in overt diabetic nephropathy. This is not an insignificant amount. If we focus on the most severe cases, where the eGFR was < 20, at week 52, the eGFR increased by 16.1 ml/min in the Avacopan group compared to only 7.7 ml/min in the Prednisone group. At the last followup at 52 weeks, 41% of the Avacopan patients and 13% of the Prednisone patients had a twofold increase in their baseline eGFR. Albuminuria also fell more quickly in the patients treated with Avacopan suggesting the renal disease resopnded much more quickly to this treatment than with Prednisone. These superior results suggest that Avacopan works better where it matters the most, in the most serious renal cases. Serious adverse events were also much lower in the Avacopan group at 48% compared to 70% in the Prednisone group. This was because glucocorticoid exposure was 63% lower in the Avacopan arm over the 52 weeks.

One other criticism CADTH had was that the rituximab was not used as maintenance therapy in the ADVOCATE Trial and patients induced with IV rituximab did not receive any maintenance therapy.

At the time of the study design in 2017, Rituximab was not given as maintenance therapy, only induction therapy. To this date, Rituximab has not been approved by Health Canada for maintenance therapy, even though it is recognized internationally as a standard of care for maintenance. Access to Rituximab as maintenance therapy remains problematic in Canada and not all jurisdictions provide coverage for Rituximab as maintenance. Even looking at the results at 26 weeks, the patients on Avacopan were already doing better than the ones on Prednisone. We are dealing with a disease where there is a high burden of disease and existing therapies are insufficient. We should be embracing new technologies and not excluding them because we would like to rewrite the protocols six years later.

| Expert committee consideration of the stakeholder input | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
| | No | ☐ |
| | | |
| **Clarity of the draft recommendation** | | |
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☐ |
| | No | ☒ |
| If not, please provide details regarding the information that requires clarification.<br><br>Please refer to point 1 above. | | |
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☐ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☐ |
| | No | ☐ |
| If not, please provide details regarding the information that requires clarification. | | |

[a] CADTH may contact this person if comments require clarification.

## Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

| A. Assistance with Providing the Feedback | | |
|---|---|---|
| **2. Did you receive help from outside your clinician group to complete this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **B. Previously Disclosed Conflict of Interest** | | |
| **4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.** | No | ☐ |
| | Yes | ☒ |
| If yes, please list the clinicians who contributed input and whose declarations have not changed: | | |

### C. New or Updated Conflict of Interest Declarations

| New or Updated Declaration for Clinician 1 | |
|---|---|
| **Name** | *Dr Robert Ting, MD, FRCP(C), FACP* |
| **Position** | *SHN Nephrologist, DMC Markham Medical Director, SHN Glomerulonephritis Clinic Specialist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

| Conflict of Interest Declaration | |
|---|---|
| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | |
| **Company** | **Check Appropriate Dollar Range** |

| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
|---|---|---|---|---|
| *AstraZeneca* | ☐ | ☐ | ☒ | ☐ |
| *Otsuka* | ☐ | ☒ | ☐ | ☐ |
| *GSK* | ☐ | ☒ | ☐ | ☐ |
| *Bayer* | ☐ | ☒ | ☐ | ☐ |
| *Boehringer* | ☐ | ☒ | ☐ | ☐ |
| *Janssen* | ☒ | ☐ | ☐ | ☐ |
| *Novo Nordisk* | ☒ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 2 | |
|---|---|
| **Name** | *Dr Paul Tam, MD, FRCP (C), FACP* |
| **Position** | *SHN Nephrologist, SHN Nephrology Chief & Medical Director-Scarborough Regional Dialysis Program* |
| **Date** | *27-04-2023* |
| ☒ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
| *AstraZeneca* | ☒ | ☐ | ☐ | ☐ |
| *Otsuka* | ☒ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 3 | |
|---|---|
| **Name** | *Dr Janet Roscoe, MD, FRCP (C), FACP* |
| **Position** | *Associate Professor Toronto* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |

| | | | | |
|---|---|---|---|---|
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 4** | |
|---|---|
| **Name** | *Dr Gordon Nagai, MD, FRCP(C)* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| **Company** | **Check Appropriate Dollar Range** | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Otsuka* | ☒ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 5** | |
|---|---|
| **Name** | *Dr Jason Fung, MD, FRCP(C)* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| **Company** | **Check Appropriate Dollar Range** | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 6** | |
|---|---|
| **Name** | *Dr Andy Zhang, MD, SHN Glomerulonephritis Clinic Specialist* |

| | |
|---|---|
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 7** | |
|---|---|
| **Name** | *Dr Tabo Sikaneta, MD* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 8** | |
|---|---|
| **Name** | *Dr Denise Tam, MD* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 9 | |
|---|---|
| **Name** | *Dr Simon Tsui, MD* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 10 | |
|---|---|
| **Name** | *Dr Andrew Wong, MD* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 11 | |
|---|---|
| **Name** | *Dr Ryan Pratt, MD* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 12 | |
|---|---|
| **Name** | *Dr Steve Wong, MD, SHN Glomerulonephritis Clinic Specialist* |
| **Position** | *SHN Nephrologist* |
| **Date** | *27-04-2023* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

To the CADTH Canadian Drug Expert Committee (CDEC),

We write to you to express our concern about the recent CADTH recommendation that avacopan not be reimbursed as adjunctive treatment for adult patients with severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in combination with standard background therapy. As Manitoba clinicians well versed in the treatment of patients with AAV, we feel the decision reflects a misunderstanding of the background and protocol of the ADVOCATE trial[1], the prior evidence base in AAV, and does not accurately represent the results of the trial and the role avacopan plays in the treatment of AAV. This recommendation ultimately does a disservice to patients, and disadvantages Canadians living with this rare, life-threatening disease, as compared to their American and European counterparts. We have elected to address relevant discussion points in the recommendation individually below.

The recommendation states that it is uncertain whether the eGFR difference between treatment groups is clinically meaningful. We would direct the committee to figure S3 and point out that for individuals with eGFR <30 mL/min, the mean difference in eGFR improvement was 5.5 mL/min. This difference is extremely clinically meaningful. A subanalysis of the Chronic Renal Insufficiency Cohort (CRIC) Study demonstrated that each 5 mL/min decrease in eGFR was associated with a 54% relative-risk increase in kidney failure, and a 23% relative-risk increase in cardiovascular events[2]. Using common tools seen in clinical practice, if the mean age and mean urine ACR from ADVOCATE, along with the achieved mean eGFR at the end of the trial are inserted into the Kidney Failure Risk Equation[3], this translates to a 14.68% 5-year risk of kidney failure in the avacopan group, versus a 25.38% 5-year risk in the prednisone group. These results are accentuated when examining the patients with eGFR <20 mL/min, where the avacopan group experienced a 16.3 mL/min increase in eGFR as compared to a 9.2 mL/min increase in the prednisone group, a difference of 7.1 mL/min. This is an incredible achievement, producing a massive reduction in kidney failure risk for those patients whose risk is the highest. Given the cost of in-centre hemodialysis in Canada is approximately $100,000 per patient per year[4], use of avacopan in patients with the most severe kidney involvement and its resulting prevention of kidney failure would likely result in tremendous long-term savings for the Canadian health-care system. In addition to the impressive magnitude of this finding, it is also worth noting its novelty. No AAV drug trial has been able to demonstrate a difference in kidney function between treatment groups at the end of trial follow up, and therefore this result is remarkable, making avacopan a critical component of therapy for patients with severe kidney involvement of AAV. This is also the result likely to be most important to patients. The Standardized Outcomes In Nephrology – Glomerular Diseases (SONG-GD) initiative identified that the most important outcome to patients with glomerular diseases such as AAV is maintenance of kidney function[5]. Thus, given the incredible improvement in eGFR seen in the patients with the most severe kidney disease, it is critical that patients with severe kidney involvement have access to this medication and its benefits in reducing kidney failure risk.

The CDEC discuss the use of non-protocol glucocorticoids between groups, refer to them as “deviations from the protocol” and imply that this makes any differences difficult to interpret. Therefore, we feel it is important to clarify a few of these points. Firstly, at baseline, the mean

prednisone equivalents received by the avacopan group totaled 654 mg, which is easily explained. During the screening period, as per the protocol, patients could receive pulses of intravenous methylprednisolone (typically 500 to 1000 mg per pulse) as well as oral glucocorticoids, with caps on total doses received. This is standard in a vasculitis trial and mandating that patients could not receive any pre-trial glucocorticoid is frankly unrealistic, as patients with AAV are typically very sick at presentation and delaying therapy to facilitate randomization would make enrolment challenging. Secondly, the remainder of the non-protocol glucocorticoids received during the treatment period are largely explained by two other sources specified in the protocol. For patients treated with rituximab, as a standard of care they receive methylprednisolone with each injection to prevent hypersensitivity reactions. Typically, this is a dose of 100 mg per injection, for a total of 400 mg during the trial, or 500 mg prednisone equivalent. This is reflected in table S5 of the trial Supplementary Appendix. Again, expecting a protocol to forbid the use of glucocorticoids at the time of rituximab administration is unrealistic and would dissuade investigators from enrolling patients. In addition, patients assigned to avacopan received tapering prednisone over four weeks, tapering from 20 mg by 5 mg per week, typically totaling 350 mg. The total of these three sources of glucocorticoids is approximately 1,504 mg when using the mean baseline prednisone received by the avacopan group. Therefore, almost all the non-protocol glucocorticoid used in the avacopan group was used in the first 4 weeks of the trial, and any further prednisone that was prescribed was likely used for symptoms of adrenal insufficiency, as was allowed in the protocol. The CDEC indicate that more non-protocol glucocorticoid was used in the avacopan group as compared to the prednisone group, and that "it is also unclear if these doses are high enough to effectively treat ANCA-AV or cause additional adverse effects." This increase in glucocorticoid received is easily attributable to the extra 350 mg received by the avacopan group during tapering of non-study prednisone. Given that AAV is typically treated with a minimum of 6-18 months of glucocorticoids, this is very unlikely to be a high enough dose or a long enough duration of therapy to effectively treat ANCA-AV over a 52 week follow up.

The CDEC also express concerns about the validity of the results of the trial based on the use of protocolized prednisone tapering in the prednisone group. We disagree with this assessment, since the comparators in the trial are avacopan and prednisone, and to be able to evaluate them properly, the groups need to be treated uniformly. Furthermore, this is not atypical for other trials in AAV examining glucocorticoid use such as PEXIVAS[6], which used aggressive protocol-driven prednisone tapering to evaluate the efficacy of two different steroid regimens. If clinicians were allowed to adjust prednisone dosing however they wished based on clinical activity, then comparison of the two groups would be impossible, as remission could simply be present because patients remained on high-dose prednisone, which is otherwise undesirable.

The CDEC express concern that the differences in adverse events between groups were not as large as expected. This is also surprising, as it is important to recognize that patients still received methylprednisolone pulses, and most importantly powerful immunosuppressants such as rituximab and cyclophosphamide, which carry significant risks of infection on their own[7] and have been documented to profoundly reduce response to vaccination[8]. Most of the difference seen with respect to adverse events is in improvements in GTI, understanding that the

minimum clinically important difference (MCID) for the GTI is 10[9]. The MCID was reached by avacopan-treated patients in both the Cumulative Worsening Score as well as Aggregate Improvement Score in the trial, demonstrating a clinically relevant reduction in glucocorticoid toxicity, which is important to patients[5]. While we understand that this tool has not been specifically validated for this rare disease, we would also ask the committee to recognize the difficulty in quantifying steroid-associated side-effects in a trial setting, and the lack of any validated tool to do so. The GTI, which was developed by internationally recognized experts in AAV, represents the best attempt yet to quantify the complex toxicities associated with glucocorticoids. It has been employed in over 45 studies including 12 phase 3 clinical trials, and has been validated in asthma[9]. The attempt by the investigators to use the GTI in this setting will pave the way for further trials in AAV and other autoimmune diseases to do the same. The trial also reported a 7.5% absolute risk reduction in treatment-emergent infections, which we feel would not be insignificant to patients.

The CDEC express concern that the instruments used in ADVOCATE, such as BVAS and VDI, are not used in clinical practice. We agree that these are not routinely used clinically but would point the attention of the CDEC to all other AAV induction and maintenance trials, where complete remission (defined by a BVAS of 0) is typically the primary outcome, with VDI frequently being a secondary outcome[10–14]. Therefore, this is not a valid criticism. In addition, they note the small differences in secondary outcomes with wide confidence intervals. It is critical to recognize that the trial was not specifically powered to detect differences in these outcomes, and that to expect sufficient recruitment to detect differences in these outcomes with narrow confidence intervals is unrealistic for a disease with an annual incidence of approximately 15 per million population.

The recommendation states that the clinical expert indicated avacopan would be used for two years. We do not agree, and would highlight the recently published CanVasc and EULAR guidelines on the treatment of ANCA-associated vasculitis, which recommend the use of avacopan for only one year[15,16]. Avacopan currently is indicated as a part of induction immunosuppression and at this time there is no evidence to inform use past one year. Therefore, assuming two years of therapy in the economic analysis is invalid.

While the above points are important, we feel the most crucial element of the CADTH recommendation is the input from Vasculitis Foundation Canada, who received feedback from 46 patients with AAV. They reported an urgent need for treatment that improves symptoms and quality of life that would also result in a reduction or elimination of the use of prednisone. We treat these individuals every day, see the impact months of high-dose prednisone can have and agree with this sentiment. We feel that placing the priorities of patients at the forefront of this decision is paramount.

The newly published EULAR and CanVasc guidelines both recommend that avacopan can be used as a component of therapy for remission induction in AAV. As clinicians, we must be able to provide guideline directed therapy to our patients, many of whom are prolific consumers of information about their disease, and who will expect access to therapies recommended by the

guidelines. This recommendation will result in a tiering of care for AAV, allowing the prescription of avacopan for those with the means to have private health coverage or pay out-of-pocket, while excluding those who are already marginalized in our society. We believe CADTH has a responsibility to try to limit these inequities and ensure access for the patients who need it. We implore you to reconsider this decision and re-examine the evidence with the points we have provided.

Sincerely,

Drs. Bryce Barr and David Robinson
Vasculitis Clinic
University of Manitoba

Bryce Barr has served on an advisory board for Otsuka Canada Pharmaceuticals and has received less than $3,000 in honoraria. We otherwise report no other relevant COI.

References


1. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med*. 2021;384(7):599-609. doi:10.1056/nejmoa2023386
2. Ku E, Xie D, Shlipak M, et al. Change in Measured GFR Versus eGFR and CKD Outcomes. *J Am Soc Nephrol*. 2016;27(7):2196-2204. doi:10.1681/ASN.2015040341
3. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305(15):1553-1559. doi:10.1001/jama.2011.451
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# Waterloo Rheumatology

435 The Boardwalk Ste 208,
Waterloo ON N2T 0C2
www.WaterlooRheumatology.com

**Dr. Yan Yeung**, MD FRCPC [redacted]
**Dr. Sabrina Lue**, MD FRCPC [redacted]
**Dr. Sandeep Dhillon**, MD FRCPC [redacted]
**Dr. Gabriel Jeyasingham**, MD FRCPC [redacted]


**April 26/2023**

**To**: The Canadian Agency for Drugs and Technologies in Health

Re: CADTH draft recommendation to not reimburse avacopan for the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)- associated vasculitis

This letter, on behalf of Waterloo Rheumatology, summarizes our position on the use of avacopan for the treatment of ANCA-associated vasculitis (AAV) and calls for reconsideration of the decision to not reimburse avacopan in Canada. We are a centre of care for rheumatology in Waterloo, Ontario.

Reducing glucocorticoid exposure is an important principle for the management of ANCA-associated vasculitis (AAV). The currently recommended induction treatment for severe disease is glucocorticoids combined with cyclophosphamide or rituximab. This treatment, however, is still associated with high mortality (mainly driven by infection and treat-related risks), and high morbidity due to steroid related events (diabetes, obesity, osteoporosis, psychiatric, infectious, cardiovascular and associated renovascular disease).

Thus, reducing glucocorticoid exposure is a crucial principle in AAV management. Avocopan is the only agent to date to have shown a substantial reduction in the use of glucocorticoids, without decreasing the rate of sustained remission. Data suggests greater sustained remission rates and better renal recovery when using avacopan

CanVasc and other international groups have identified the importance of avacopan in the current therapeutic strategy for GPA and MPA (Turgeon et al. Rheumatology 2023). CanVasc is a not-for-profit organization consisting of representatives from clinical and research centers across Canada with an expertise in vasculitis. Since then, the European Alliance of Associations for Rheumatology (EULAR) group also published a recommendation on avacopan for the management of ANCA-associated vasculitis (Hellmich et al. Ann Rheum Dis 2023), while the drug is being incrementally approved in several countries in Europe for reimbursement (France, UK)

Avacopan as adjunctive therapy for adults with severe AAV (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapies has been approved by Health Canada, the FDA in the USA and agencies in Europe. For this approved use, avacopan is now being prescribed globally

Based on the available evidence (3 randomized controlled trials and 2 observational studies), we recommend:

1. The addition of oral avacopan (30 mg twice daily) can be considered for induction of remission in patients with newly diagnosed or relapsing GPA or MPA treated with cyclophosphamide or rituximab
2. After starting avacopan, a faster glucocorticoid tapering protocol aiming for discontinuation by the end of week 4 should be considered
3. When initiated as part of induction therapy, avacopan can be continued for one year

There is a role for avacopan in the treatment of patients with severe GPA or MPA. There is no alternative or equivalent agent available to date in Canada that would achieve such a substantial steroid-sparing effect and may additionally help maintain remission and improve renal outcomes. Patients are now aware of this agent, its expected benefit and current use abroad. We are concerned that the CADTH recommendation to not reimburse avacopan will disproportionately affect access to this drug in Canada for low income and marginalized populations. The limitation in the use of avacopan in Canada will also impact research on this agent, while registries have been initiated now in Europe and USA where access to drug has been approved.

Sincerely,

[redacted]

Dr. Yan Yeung, MD FRCPC
Rheumatologist, Waterloo Rheumatology
Assistant Clinical Professor (Adjunct),
McMaster University
[redacted]

[redacted]

Dr. Sabrina Lue, MD FRCPC
Rheumatologist, Waterloo Rheumatology
Assistant Clinical Professor (Adjunct),
McMaster University
[redacted]

[redacted]

Dr. Sandeep Dhillon, MD MSc FRCPC
Rheumatologist, Waterloo Rheumatology
Assistant Clinical Professor (Adjunct),
McMaster University
[redacted]

[redacted]

Dr. Gabriel Jeyasingham, MD FRCPC
Rheumatologist, Waterloo Rheumatology
[redacted]

**References**:


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# CADTH Reimbursement Review

# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0732 |
| Name of the drug and Indication(s) | Avacopan (Tavneos) for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. |
| Organization Providing Feedback | FWG |

| 1. Recommendation revisions<br>Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation. | | |
|---|---|---|
| **Request for Reconsideration** | **Major revisions:** A change in recommendation **category** or patient **population** is requested | ☐ |
| | **Minor revisions:** A change in reimbursement **conditions** is requested | ☐ |
| **No Request for Reconsideration** | **Editorial revisions:** Clarifications in recommendation **text** are requested | ☐ |
| | **No requested revisions** | X |

| 2. Change in recommendation category or conditions<br>Complete this section if major or minor revisions are requested |
|---|
| Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation. |

| 3. Clarity of the recommendation<br>Complete this section if editorial revisions are requested for the following elements |
|---|
| **a) Recommendation rationale** |
| Please provide details regarding the information that requires clarification. |
| **b) Reimbursement conditions and related reasons** |
| Please provide details regarding the information that requires clarification. |
| **c) Implementation guidance** |
| Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. |

# CADTH Reimbursement Review
# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0732-000 |
| Brand name (generic) | Avacopan (Tavneos) |
| Indication(s) | GPA and MPA ANCA Associated Vasculitis |
| Organization | Vasculitis Foundation Canada |
| Contact information[a] | Jon Stewart |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | ☒ |

From the rationale and recommendation paragraph.

**Unmet Therapeutic Need**

The ADVOCATE trial explains "C5a production, is a component of the pathogenesis of ANCA-associated vasculitis" and that Avacopan is a "C5a receptor antagonist that selectively blocks the effects of C5a… including blocking neutrophil chemo-attraction and activation." **No other medication works on this pathway of the pathogenesis of AAV, so this must be an unmet need! How can you justify that this is NOT?**

**The Real Unmet Need**

Canadian vasculitis patients know what they do not like about prednisone. They also know, as do most Canadians with rare diseases, the **real unmet need for Canadian patients is that Canada has a chronic problem of timely approvals of new therapies compared to the FDA or EU**. And, **equally important is access and coverage for newer medications that cost more**. Many rare disease therapies are inherently more expensive due to the small size of the patient population that will consume them. The costs to develop and bring to market a new medication is similar regardless of whether thousands, or tens of thousands of people take it, compared to if only hundreds of patients take a given medication. **The economies of scale do not favour medications for rare diseases, this is another unmet need!**

**Rituximab for Maintenance Therapy**

**Although rituximab (RTX), may be the current standard of care, it is not the current practice of care for all Canadian patients!** In Canada, "postal code healthcare" is a well-known fact-of-life, and rituximab, or more frequently now biosimilars, are not even approved for maintenance, or for induction based on age, gender etc., in many provinces and territories. Nor are they universally publicly funded for those in need. In reality, **CYC and azathioprine (AZA), as prescribed in the ADVOCATE study, does align with the Canadian standard of care for many AAV patients.**

**Infection and Rituximab and Glucocorticoids (GC/Prednisone)**

Even if all AAV patients could access RTX, reliance mainly on RTX therapy, has other complications. **RTX significantly impairs vaccine uptake which has obvious negative impacts on AAV patients during a pandemic,** or anytime they require any vaccine. **This is another unmet therapeutic need.** Excess treatment with both RTX, and prednisone at doses of +/- 20mg's/day, impairs vaccine uptake. **High rates of infection in the AAV community is an unmet need, and avacopan can help mitigate this.**

**Non-protocol Specified Glucocorticoids (GC's/prednisone)**

Using non-protocol prednisone was the point of the study in one arm to test the efficacy of Avacopan. How else could this arm be done? The second arm essentially received a similar "reduced-dose" prednisone taper as was used, with success, in the PEXIVAS trial. **The study goal was to reduce prednisone exposure, without losing disease control, which aligns with the unmet needs of patients.**

**Equity in Healthcare**

We note that in 2018 CADTH approved Tocilizumab (TCZ-Actemera), for GCA, another form of life-threatening vasculitis for a 52 week treatment course, the same time period in the ADVOCATE trial for

Avacopan. It was noted then "the costs attributed to the complications of prednisone therapy are highly uncertain" and "that an important goal of therapy with tocilizumab is related to the benefit of preventing morbidities associated with chronic-moderate to high dose glucocorticoids." **this key goal aligns with the ADVOCATE trial.** There are more similarities including a rapid prednisone taper, and the use of "escape prednisone". **We have shown in our original submission the complications of prednisone therapy are well known for patients with AAV yet Avacopan has not been approved - even with conditions! This non-approval is ill advised and not equal treatment by CADTH for vasculitis patients with AAV. Reducing prednisone exposure remains an unmet need across all vasculitis conditions**, and **real progress towards addressing this unmet need must be taken for all forms of vasculitis -** when available.

**Expert committee consideration of the stakeholder input**

| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
|---|---|---|
| | No | ☒ |

**Lack of Canadian Access Cascades into Lack of Healthcare**

When Canadian patients are denied access to modern mediations like Avacopan, or face unreasonable barriers to pay to access Avacopan, specialist physicians are also deprived of new therapy options to treat lethal diseases. And, **oral Avacopan is easier for patients to manage compared to the more complicated, more costly to administer, and much more time consuming therapy of RTX infusions over multiple hours in hospital or specialized clinics.**

**Additional Real-World Evidence and Patient Input**

Vasculitis is a rare disease. Vasculitis Foundation Canada engages with a large vasculitis community in Canada. **Our emails are sent regularly to a list of ~400 members and friends, we have 1500 followers on our Facebook page and another 580+ in our private Facebook Group page.** There are small numbers of Canadian Avacopan users so we felt it essential to ask for, and include, additional real world evidence and feedback from **Canadian patients on Avacopan who wrote to us.** See **Appendix #1 and #2.**

**We believe Avacopan is the next breakthrough in AAV therapy, and we want Canadians with AAV, who do not have full coverage for Avacopan, to receive public coverage of this therapy as experienced by Patient #1 and #2 below.**

**VFC recommends that Avacopan be reimbursed for the treatment of AAV if the following conditions are met, in the words of your own consultant, who suggested "that alongside the implementation of avacopan in Canada it would be useful to set up a registry to track drug use, patterns of use, and to monitor safety and efficacy." This approach contributes and builds valuable real world evidence on Avacopan while addressing numerous unmet needs for Canadian AAV patients without a significant budget impact.**

**Appendix #1 & #2 from Patients #1 & #2** These letters are self-explanatory, but we have highlighted some key points that reinforce points we have made. These are convincing success stories of real world Avacopan evidence. **Patient #1 reports "Avacopan has changed his life"** while on standard background therapy of Rituximab (RUXIENCE), and a rapid prednisone taper. **Patient #2 reports** "I think the Avacopan has been amazing. **Her quality of life wouldn't be near what it is if she was still on prednisone**. The **prednisone was saving her from the Vasculitis, but killing her in other ways."**

**Appendix #1 CADTH Feedback (Patient #1 with MPA Vasculitis, April 2023, edited to save space)**

I was asked to write a letter with my first hand experience with TAVENOS- Avacopan. I am a very active 36 year old Male with no pre existing health conditions and no significant family history of auto-immune diseases. I am a am active with daily lifting weights, cardio, and sports. I am also on a tactical team with a [redacted] law enforcement agency; which is very physically demanding.

Sometime in August 2022 I developed a persistent fever of unknown origin. In late September I developed severe leg cramps. Some days it was impossible to walk around at a normal pace. I originally thought my symptoms were a combination of a viral/bacterial illness and delayed onset muscle soreness from lifting weights. After three weeks of symptoms I attended [redacted] Physician. I was sent to the hospital for bloodwork and sometime that evening was told to report to Emergency as it was suspected that I had possible blood clots. I was in the hospital for approximately 7 days, I was prescribed Prednisone and sent home. The prednisone helped alleviate symptoms; however, it came with many side effects. I was improving

but my quality of life was not the same. I was placed on modified duties at work due to my side effects as I was unable to complete my daily tasks without issues.

I attended [redacted] Rheumatology clinic, it was explained they had a high suspicion of ANCA Associated Vasculitis(MPA). The disease appeared to be attacking my small blood vessels, kidneys, and arthritis in my joints. I had blood and frothing in my urine and the arthritis was still affecting my joints. I was prescribed a heavy dose of Prednisone, antibiotics, and was told that I would be receiving RUXIENCE-Rituximab in November.

Over the next few months I continued to display mild symptoms, weight gain, and my quality of life was still not back to normal. My urine was still frothy with trace amounts of blood. I was not sleeping well, had joint pain, headaches, and I felt weak and fatigued most of the time. I was dosed with RUXIENCE in November and early December. My side effects continued to persist. I was told at this point that I would be receiving the drug TAVNEOS-Avacopan. I Started taking Avacopan late December and was very aggressively tapered off of Prednisone. After a few weeks on Avacopan I felt like my quality of life was back to where I was pre-disease. I was shocked with how fast this drug worked for me. Before Avacopan I wasn't able to lift weights without pain and had no energy to run or ride my bike.

A week following taking my first Avacopan dose I noticed my energy levels return to normal. I was getting quality sleep and I was back to being able to lift very heavy weight in the gym and was back to my normal 5k runs twice a week. My joint pain had completely disappeared and my kidneys have been normal functioning again. My urine looks normal. I am able to do my job at work again with the tactical team. I am able to play with my kids without any pain or having to cut activities short. The only symptom that continued after Avacopan was the purple patches on my skin, which used to be very vivid and unsightly. Now they are barely distinguishable and I noticed that they only appear after rapid temperature changes. I have also noticed since being on Avacopan my weight has been slowly returning to my healthy weight prior to receiving my first doses of Prednisone.

I was placed on Avacopan for one year as a trial. I was offered other drugs; however because I am still thinking of having more children this was the safest drug with the least amount of reproductive harm. My last appointment was on 2023-04-20. I was informed that Avacopan will not be covered after the trial. This drug is expensive and no middle class person can afford the drug without a substantial drug plan. I feel that this drug should be on the list of preferred drugs to be used for ANCA Associated Vasculitis. The results are truly amazing from my perspective. I am fairly new to the ANCA Vasculitis community and there is no one I know that is completely asymptomatic like myself and the only noticeable difference between myself and them is Avacopan.

In conclusion Avacopan has changed my life. After my diagnosis I was scared, depressed, and thought the rest of my existence was going to be limiting. Six months later I feel like there is nothing I cannot accomplish. I have been able to enjoy all activites/work prior to my diagnosis and initial treatment. I have a great outlook towards life and a hopeful future.

**Appendix #2** (Mother of Patient #2, 14 year old girl with GPA Vasculitis, April 2023, edited to save space)

Avacopan is essential for people with Vasculitis. Yet it is so expensive, no one could afford to take this life saving drug without coverage/funding. The idea that they want to make it un-accessible for people is unfathomable. She has upper airway (trachea) and lung involvement and tolerated Avacopan extremely well. Some stomach upset the first few days, but then it settled. No other side effects. She was given dozens of high dose pulse prednisone IV's over many months. And also took oral prednisone for approx 9 months. The steroids caused massive damage to her skin; she has stretch marks from her mid back to her ankles. She had hair loss. Severe moon face. She developed GERD. She has done very well on Avacopan. All of her disease markers have remained negative since she tapered off prednisone and is only on Avacopan. She finished her last dose of prednisone on Feb 3. I think the Avacopan has been amazing. Her quality of life wouldn't be near what it is if she was still on prednisone. The prednisone was saving her from the Vasculitis, but killing her in other ways.

## Clarity of the draft recommendation

| | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☐ |
| | No | ☒ |

The ADVOCATE trial explains "C5a production, is a component of the pathogenesis of ANCA-associated vasculitis" and that Avacopan is a "C5a receptor antagonist that selectively blocks the effects of C5a… including blocking neutrophil chemo-attraction and activation." **No other medication works on this pathway of the pathogenesis of AAV, so this must be an unmet need! How can you justify that this is NOT?**

| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☐ |
|---|---|---|
| | No | ☒ |

**Lack of patient registries in Canada**

**Since national patient registries are another unmet need in Canada,** determining the accurate number of annual AAV patients, and the total number of AAV patients in Canada is unknown. In the absence of accurate data, **we agree with the CADTH clinical expert who suggested "that alongside the implementation of Avacopan in Canada it would be useful to set up a registry to track drug use, patterns of use, and to monitor safety and efficacy." This can address many unmet needs, and other unknowns including costs and benefits."**

| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☐ |
|---|---|---|
| | No | ☒ |

**Budget Impact**

There is evidence to suggest that patients with rare diseases receive only 2.4% of total public pharmaceutical expenditures yet represent more than 2.4% of the population. Minister Duclos recently announced 1.5 billion for rare diseases. We think the total budget impact is relatively small over 3 years and more needs to be done to approve and publicly pay for new therapies like Avacopan for the treatment of AAV. Putting a value on the cost of life is not easy, but AAV patients deserve a better chance to regain their health, and return them to more productive lives. Avacopan appears to do that. **The reality is that very few Canadians could afford to pay out-of-pocket for Avacopan which is another unmet need for Canadians** for those without full private insurance coverage. **Those excluded from gaining the benefits of Avacopan will experience the full impact of the inequity of Canadian healthcare which already has its share of inequities.** And, **it is worth noting the cost of Avacopan in Canada is estimated to be half the price of Avacopan in the U.S.** This being the case, it is difficult to justify the lack of public coverage for Canadians given such a price advantage. **Canada is supposed to be a "first-world", G7 country**, yet recent changes to the PMPRB eliminated Switzerland and the U.S. from our basket of comparator countries on drug pricing. Eliminating these countries was estimated to generate overall drug savings of +/- 20% in Canada. **With these savings, how is it possible Canada cannot publicly fund Avacopan while it funds equal or more expensive therapies?**

[a] CADTH may contact th s person f comments requ re c ar f cat on.

## Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

| **A. Patient Group Information** | |
|---|---|
| **Name** | *Jon Stewart* |
| **Position** | *President* |
| **Date** | *(27-04-2023)* |
| ☒ | I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation. |

| **B. Assistance with Providing Feedback** | | |
|---|---|---|
| **1. Did you receive help from outside your patient group to complete your feedback?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |

| **C. Previously Disclosed Conflict of Interest** | | |
|---|---|---|
| **1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.** | No | ☒ |
| | Yes | ☐ |

**D. New or Updated Conflict of Interest Declaration**

**3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.**

| **Company** | **Check Appropriate Dollar Range** | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| Otsuka Canada Pharmaceutical Inc. | ☐ | ☐ | ☐ | ☒ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |