NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Vifor Pharma**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Vasculitis UK
   b. British Society for Rheumatology (endorsed by Royal College of Physicians)
   c. United Kingdom and Ireland Vasculitis Society

4. **Evidence Review Group critique of company comments on the ACD**

There were no comments submitted by the nominated experts or submitted through the NICE website. Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		Vifor Pharma	Section 2.1 - Marketing authorisation indication We request that the committee's recommendation should take into consideration that the MRHA has granted avacopan (Travneos) marketing authorisation with orphan status. In qualifying for orphan designation the MHRA have acknowledged the following: • Severe and active GPA and MPA is a chronically debilitating, life threatening disease. • The number of patients with severe active GPA and MPA eligible for an avacopan-based regimen in England each year (n=1,346) is significantly less than the orphan drug threshold of 5 in 10,000. • Avacopan is of significant benefit to those affected by severe active GPA or MPA	Thank you for your comment. The committee recognised that GPA and MPA are rare conditions that can be associated with severe symptoms. Please see section 3.1 of the FAD. The committee also concluded that avacopan with a cyclophosphamide or rituximab regimen was effective at sustaining disease remission and reducing corticosteroid-induced toxicity compared with a prednisone-based regimen in the intention-to-treat population of ADVOCATE. Please see section 3.6 of the FAD.
2		Vifor Pharma	Section 2.3 – Price The list price for avacopan (Tavneos) has been approved by DHSC, therefore it is no longer confidential. The list price for avacopan (Tavneos) is £5,547.95 for a 180 pack of 10mg capsules.	Thank you for your comment. The FAD has been updated to include the list price for avacopan. Please see section 2.3 of the FAD.
3		Vifor Pharma	Section 3.1 – "The committee recognised that people with severe active GPA or MPA can have severe symptoms" Section 3.2 – "The committee concluded that people with GPA or MPA, and clinicians, would welcome a new treatment option that could reduce the need for corticosteroids" Section 3.6 – "The committee concluded that avacopan was effective at sustaining disease remission and reducing corticosteroid-induced toxicity compared with a prednisone-based regimen in the intention-to-treat population of ADVOCATE" We agree that patients with GPA and MPA can have severe symptoms and that avacopan is effective at sustaining disease remission and reducing corticosteroid toxicity; however, the ACD does not recognize the full extent of the morbidity and mortality associated with AAV and the substantial impact this has on patients'	Thank you for your comment. The FAD has been updated to reflect that people with GPA and MPA can have severe symptoms and the conditions can be life threatening. Please see section 3.1 of the FAD. The committee also concluded that avacopan with a cyclophosphamide or rituximab regimen is effective in sustaining disease remission and reducing corticosteroid toxicity in the intention-to-treat population. Please see section 3.6 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			quality of life. Therefore, it does not take into account the likely long-term benefits of sustained disease remission and reduced corticosteroid toxicity of an avacopan-based regimen. As outlined in the original company submission, AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patient morbidity, mortality, and quality of life (QoL). Despite current standard of care (SoC) treatment, the mortality rate in GPA and MPA patients remains higher than that of the general population. Longer-term mortality in AAV is increased because of disease-related complications, development of cardiovascular (CV) disease, renal disease, and corticosteroid-related toxicity. In addition, in current management pathways, the risk of corticosteroid-mediated morbidity is likely to increase with each occurrence of relapse. The ACD included comments from one NICE clinical expert stating that infection and cardiovascular disease, which are the most common causes of death in this population, are both associated with corticosteroid use. However, within the ACD the committee does not explicitly recognise how the benefits of reduced corticosteroid usage associated with an avacopan-based regimen will address this current unmet need in AAV and the likely long-term benefits. The ACD also underappreciates the impact of AAV on patients' quality of life. The original company submission highlighted how the chronic relapsing and remitting nature of AAV, requirement for prolonged treatment and corticosteroid-related adverse events, significantly impacts patients' physical and emotional well-being, reducing their quality of life. Despite this, the ACD only references patient and clinical experts commenting on the side effects and toxicity of corticosteroids with regards to improvements in quality of life, and not the quality-of-life improvements associated with sustained disease remission. To our knowledge, ADVOCATE is the only study in AAV that has demonstrated a positive impact of a treatment on patient quality of life. In summary, an avacopan-based regimen provides an effective and needed treatment option for the management of MPA and GPA over the current SoC, as demonstrated by reduction in relapses, statistically significant increase in sustained remission rates, reduced corticosteroid usage and associated adverse events, improvement of renal function, and improvement in patients' QoL.	
4		Vifor Pharma	The company agree with the committee recommendation in Section 3.10 that the ERG scenario overestimated the proportion of patients who are expected to receive rituximab maintenance in clinical practice. The company have submitted a revised version of the model which includes results based on an assumption that 35% of patients with previous rituximab induction treatment are eligible for rituximab maintenance treatment (midpoint of the 30%-40% estimated by clinical experts, with 30% and 40% values applied in separate scenario analyses). This	Thank you for your comment. The committee considered the analyses presented by the company assuming 30%, 35%, and 40% of people who had rituximab as induction treatment had it as maintenance. It concluded all scenarios were relevant for decision making. Please see section 3.9 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			analysis is based on a weighted average of model results for the patient subgroup eligible for rituximab maintenance treatment (22.7% of ADVOCATE trial population) and those not eligible (77.3%). The inputs and results of this analysis have been included in the 'RTX maintenance analysis' tab of the updated model file.	
5		Vifor Pharma	Section 3.10 – "The ERG commented that the rituximab maintenance scenario was uncertain. It suggested that the company explore additional evidence, for example, observational data. The company did not provide this" Company response for request of additional data from the ERG to inform the analysis of rituximab maintenance: whilst there are a small number of patients in the avacopan compassionate use programme who received maintenance treatment with rituximab, there is no additional real-world evidence which could robustly inform a direct or indirect comparison which includes rituximab maintenance treatment.	Thank you for your comment. In response to consultation, the ERG noted that, in the absence of real-world observational data, the company's naive approach was pragmatic. The committee concluded the company's modelling of rituximab maintenance treatment was appropriate and considered all scenarios during decision making. Please see section 3.9 of the FAD.
6		Vifor Pharma	Section 3.11 – "[The committee] concluded that it was relevant to consider scenarios using the Gercik et al. and Brix et al. hazard ratios, both individually and pooled" The company agree with the committee recommendation that hazard ratio estimates for end stage renal disease from Gercik et al. and Brix et al. need to be considered both separately, and as a pooled estimate, due to the uncertainties involved with the pooling method. In the revised cost-effectiveness model, the company have set the pooled hazard ratio estimated by the ERG (0.947) as the base case, and presented results based on Gercik et al. and Brix et al. individually in order to characterise the impact of uncertainty around this parameter value. The company consider the pooled method to be a conservative base case, give evidence from other studies (e.g. Gopaluni et al. Arthritis Rheumatol 2019;71(5):784-91) which suggest that the true value of the hazard ratio is lower than 0.947.	Thank you for your comment. The committee concluded that the company's analyses using the individual and pooled estimates were relevant for decision making. Please see section 3.10 of the FAD.
7		Vifor Pharma	Section 3.12: "The committee concluded that the ERG's approach to hospitalisation costs was more reflective of costs in the NHS in England" The company are concerned that the estimates of hospital cost based on NHS Reference Costs 2019/20 are likely to underestimate the true cost of hospital treatment for patients with AAV in England, for the following reasons: (i) the unit cost in NHS Reference Costs represents an average across all recorded spells linked to the specific healthcare resource group (HRG), and therefore it is not reflective of the cost of long hospital spells, such as the ones observed in the ADVOCATE trial; ii) the average length of stay in the NHS Reference Costs is reflective of the overall patient population with AAV, rather than the more narrowly	Thank you for your comment. The committee noted the company's comments that the 2019/20 Reference Costs may be conservative. The committee concluded that the company's revised approach to hospitalisation costs using 2019/20 unit costs with no adjustment for excess bed days was appropriate for decision making. Please see section 3.11 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			defined target population with severe, active AAV, and therefore is likely to be an underestimate. The estimates based on NHS Reference Costs 2019/20 without adjustment for excess bed days were applied in the revised company model and should therefore be treated as conservative.	
8		Vifor Pharma	Based on the changes outlined above, the base case incremental cost-effectiveness ratio (ICER) in the company model was updated from £19,441 per quality-adjusted life-year gained to £46,465, which is consistent with the NICE committee conclusion that the most plausible ICER would likely be above the ERG's base case ICER of £40,516. To facilitate access to avacopan for the full population covered by its marketing authorisation, the company is seeking to amend the commercial arrangement in place with NHSE which updates the price of avacopan from £[redacted] to £[redacted] per 10mg capsule. The new company base case ICER with the updated price is £27,091. In scenarios which assumed that 30% and 40% of rituximab-induced patients are eligible for rituximab maintenance treatment, the ICER was £26,383 and £27,812, respectively. In the scenarios which assumed the HR for end stage renal disease based on Gercik et al. and Brix et al., the ICER was £14,668 and £31,880, respectively.	Thank you for your comment. The committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) was within the range NICE normally considers an acceptable use of NHS resources, that is £20,000 to £30,000 per quality-adjusted life year (QALY) gained. The exact ICER cannot be reported here because it includes confidential discounts for some of the comparator treatments. Please see section 3.13 of the FAD.
9		Vasculitis UK	Thank you for the opportunity to consult on the appraisal of 'Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis'. We were disappointed to learn that that the appraisal committee's current position is not to recommend the use of avacopan because of the uncertainty in the cost-effectiveness model. We hope that the committee will reconsider their recommendation, not to entertain patient's want but the patient's unmet need for effective treatment.	Thank you for your comment. Avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults. Please see section 1.1 of the FAD.
10		Vasculitis UK	There are three medications available to treat severe GPA and MPA vasculitis, cyclophosphamide, rituximab and corticosteroids. The most effective initial treatment is either a combination of cyclophosphamide and corticosteroids or rituximab and corticosteroids (starting from a high dose, therefore the toxicity is high). **There is an unmet need for new medication to:** **A/ decrease the cumulative toxicity of the medication the patients receive**. From the ADVOCATE trial we know that avacopan group had lower mean Corticosteroid Toxicity Index Cumulative Score (39.7) than the prednisone group (56.6). Side effects from steroid use translate into increase cost for NHS to treat the side effects and related morbidities. Patients must be treated for cataracts in much younger age, many get diagnosed with diabetes, osteoporosis that causes early degeneration of the spine or the hips, mental health issues and the list is endless.	Thank you for your comment. The committee recognised that people with GPA or MPA, and clinicians, would welcome a new treatment option that could sustain disease remission and reduce the need for corticosteroids. The committee recognised the side effects and toxicity of corticosteroids and noted the impact of treatment on patients' quality of life. The committee also understood that regular monitoring for the side effects by several types of clinicians can be needed. For example, people having corticosteroids for a prolonged time may regularly visit a pain clinic, an ophthalmologist and a rheumatology and orthopaedic combined clinic to manage corticosteroid side effects. Please see section 3.2 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			My consultant told me that the prolonged time I was on steroids has made my body age by 20 years. At the age of 53 I must have monthly consultations at the pain clinic for the pain caused by the generation of my spine, I have to be seen annually by an ophthalmologist (instead of seeing a private optometrist every two years), I will have to have cataract operations in both eyes in the next couple of years, I have had scans and an MRI plus many consultations in the rheumatology/orthopaedic combined clinic to find the cause of my ongoing pain that made me housebound for quite long time. Here are some comments vasculitis patients have made about the side effects from steroids: [redacted] *: I had a massive bleed was rushed into hospital, they didn't know if I would make it, had to have a blood transfusion, and was taken off them (steroids) straight away.* [redacted]*: When you mention that you've been prescribed steroids people automatically think of the swollen face, tummy and back. The extra weight suddenly appearing. When the skin is so fragile both arms and legs are covered in bruising and scars as well as presenting with muscle wastage. I would like to bring attention to how my mental health has been impacted from taking Prednisone for the past twelve years. The emotional changes I've experienced have been dramatic. My mental well-being has been severely compromised through mood swings, aggression, changes to my personality and appearance. My self esteem and, in turn, self confidence plummeted when people didn't recognise me due to the changes. One of my biggest health challenges currently is steroid-induced diabetes which is currently not controlled. Again all of this impacts how I see myself and how others view me. Without sounding dramatic, steroids almost cost me my family. The enormous changes were difficult for my husband and children to understand or accept. It was only after being prescribed quetiapine and sertraline that the family unit became more settled.* [redacted] *I was suicidal on 30mg, manic on 10mg. Reflux, glaucoma, cataracts, vertebral fractures,insomnia, weight gain, impaired judgement, musculoskeletal problems: all confirmed in clinic…* **B/ to get in remission and sustain it for longer time.** Getting in remission as fast as possible and sustain remission is very important for two reasons. It lessens the risk of organ damage caused by active vasculitis and by remaining in remission the patient doesn't have to go through the initial treatment again followed by maintenance treatment (it can be a vicious cycle: initial treatment, get in clinical remission, maintenance treatment, relapse, initial	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatment…) Sustaining remission makes the treatment more cost effective as it decreases the cost of treating the patient again with the initial treatment, the cost of closely monitoring the patient and of course decreases the need of treating side effects caused by high toxicity treatment. During the pandemic we have noticed that many of our members were advised either to postpone or change treatment f they were on Rituximab maintenance treatment because of the increased risk of getting covid and get severely ill. These patients would benefit a lot of sustaining remission and decrease the risk of needing high dose of Rituximab to get in clinical remission again. The committee has noted that clinical trial shows, that after a year, avacopan is more effective at stopping the condition getting worse than standard care (corticosteroids) and that at the week 52, 71.0% of the avacopan group had sustained remission compared to 56.1% of the prednisone group. The difference was even larger at the anti-MPO positive subgroup in which 70.2% of the avacopan group had sustained remission compared to 48.0% in the prednisone group. There are patients with refractory vasculitis that cannot take steroids as they react badly to them, for these patient avacopan could be the chance to get in remission, have a better quality of life and decrease the risk of loosing their life because of vasculitis. [redacted]*: In the past I have been prescribed prednisone to alleviate the following symptoms when my vasculitis was flaring; purpuric rash on legs, swelling, pain, generally feeling unwell and flu like symptoms. The medication did not help alleviate my symptoms but made them worse. I also had a steroid injection prior to my wedding day as I was flaring. Again, it exacerbated my flare.* [redacted]*: Prednisolone has caused me so many problems that I can't wait for an alternative drug. Even with half the side effects it would be so much better. Most of all I want a drug that gives me a break from the constant drain of inflammation, pain and fatigue that goes with my vasculitis, without major side effects. Avacopan seems to promise this, which is why I signed up for the trial. My experience of the trial was not at all good, but I still want that drug!!* [redacted] *I took prednisolone initially to control my GPA symptoms and have managed to taper off steroids, my understanding is it is not appropriate to take steroids long term due to the significant side effects. Avacopan is recommended as it is a specific drug which has been developed to control vasculitis symptoms. I was informed by my consultant that there are currently no major side effect from this drug when compared to other drugs which*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			are available. The effect of being able to take avacopan would be that my GPA is adequately controlled along with rituximab infusions. The other drugs which could be used have more side effects and not as effective.	
11		Vasculitis UK	Vasculitis is a life changing illness, and it can be life threatening. Treatment doesn't only alleviate severe symptoms, but also aims to save the life of patients. The cost of treatment is not only the financial cost for NHS, but also, they price patients pay being on toxic medication and the increased cost for NHS to treat the side effects of that treatment. Patients need to have an alternative medication that will put them in remission, but at the same time will not decrease their quality of life. As a GPA patient with lung and sinuses involvement that was severely ill at the time of diagnosis, I am grateful that the medication given to me saved my life, but I wish there was an alternative (like avacopan) that I could have taken. I was diagnosed when I was 45 years old (almost 8 years ago) much younger than the average GPA patient, but I feel like I am 70 most of the time. When I was diagnosed and asked for my prognosis, I was told by my doctor that *I will save you if I don't kill you with the medication I will give you.*	Thank you for your comment. The committee concluded that people with GPA or MPA, and clinicians, would welcome a new treatment option that could sustain disease remission and reduce the need for corticosteroids. Please see section 3.2 of the FAD.
12		Vasculitis UK	For all the reasons above we hope you will reconsider and give the option of a novel treatment to patient with severe GPA or MPA vasculitis.	Thank you for your comment. Avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults. Please see section 1.1 of the FAD.
13		UKIVAS (United Kingdom and Ireland Vasculitis Society)	**Has all of the relevant evidence been taken into account?** One reason for NICE rejection is that there is no/limited data for maintenance avacopan treatment – we agree there are no data beyond 12 months and NICE could limit approval to 12 months from flare, although for occasional difficult to control patients it will be unfortunate to stop avacopan if it is the only drug that has worked well.	Thank you for your comment. Avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults. Please see section 1.1 of the FAD.
14		UKIVAS (United Kingdom and Ireland Vasculitis Society)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The cost effectiveness model underestimated the risk of kidney failure because it used CPRD data, in which microscopic polyangiitis (MPA) is under-represented and the CPRD population misses the most severe patients, who die/go onto dialysis early and are not necessarily picked up. Data from clinical trials point to a higher kidney failure risk. Additional modelling should examine benefits of avacopan in patients with diabetes and those who are obese, where steroid-sparing is more important.	Thank you for your comment. The committee recalled that in its original analysis, the company used literature values and the ERG preferred CPRD data to estimate the probability of developing ESRD. At technical engagement, the company provided an updated approach of calibrating the model estimates using published evidence. The calibrated estimates were between the company's and ERG's original preferred values. This was considered to reflect real-world practice.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
15		UKIVAS (United Kingdom and Ireland Vasculitis Society)	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** In general, the vasculitis community have accepted the results of the ADVOCATE trials and are keen to bring these advantages to their patient population, in whom drug choice remains quite limited and toxicity high. There is a subgroup of patients with refractory ANCA vasculitis who have the highest risk for death and kidney failure, in whom an alternative therapy is needed.	Thank you for your comment. Avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults. Please see section 1.1 of the FAD.
16		British Society for Rheumatology	We are disappointed that the appraisal committee is not recommending the use of avacopan with cyclophosphamide or rituximab. Further consideration is needed to ensure more patients can access this treatment, as the effective treatment of patients with severe AAV remains an unmet clinical need, The following key issues highlight the need for this treatment: • **Reduced use of corticosteroids**: There are obvious benefits to a treatment that reduces the cumulative corticosteroid dose. It reduces the side effects and associated morbidity for patients, while also reducing the costs on trust for treating those side effects. Additionally, relapse and the resulting high-dose of corticosteroids for remission induction and increased rituximab exposure is associated with greater NHS activity and spent resources. • **Increased remission**: Rates of remission increased in the avacopan arm of ADVOCATE RCT. • **Benefits to patients**: Certain subgroups of patients benefitted, such as those with relapsed or refractory disease. It is not clear why patients who are MPO positive have benefitted clinically more that those patients who were PR3 positive. • **COVID-19 vaccine effectiveness**: There is an increased risk of non-response to COVID-19 vaccination and worse outcomes for infected patients with high dose corticosteroids and exposure to rituximab	Thank you for your comment. The committee recognised that people with GPA or MPA, and clinicians, would welcome a new treatment option that could sustain disease remission and reduce the need for corticosteroids. Please see section 3.2 of the FAD. The committee also concluded that there may be additional benefits of avacopan that may not be captured in the cost-effectiveness analysis. Please see section 3.15 of the FAD. Therefore, the committee concluded that avacopan with a cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults. Please see section 1.1 of the FAD.

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Vifor Pharma**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Section 2.1 - Marketing authorisation indication We request that the committee's recommendation should take into consideration that the MRHA has granted avacopan (Travneos) marketing authorisation with orphan status. In qualifying for orphan designation the MHRA have acknowledged the following: • Severe and active GPA and MPA is a chronically debilitating, life threatening disease. • The number of patients with severe active GPA and MPA eligible for an avacopan-based regimen in England each year (n=1,346) is significantly less than the orphan drug threshold of 5 in 10,000. • Avacopan is of significant benefit to those affected by severe active GPA or MPA
2	Section 2.3 – Price The list price for avacopan (Tavneos) has been approved by DHSC, therefore it is no longer confidential. The list price for avacopan (Tavneos) is £5,547.95 for a 180 pack of 10mg capsules.
3	Section 3.1 – "The committee recognised that people with severe active GPA or MPA can have severe symptoms" Section 3.2 – "The committee concluded that people with GPA or MPA, and clinicians, would welcome a new treatment option that could reduce the need for corticosteroids" Section 3.6 – "The committee concluded that avacopan was effective at sustaining disease remission and reducing corticosteroid-induced toxicity compared with a prednisone-based regimen in the intention-to-treat population of ADVOCATE" We agree that patients with GPA and MPA can have severe symptoms and that avacopan is effective at sustaining disease remission and reducing corticosteroid toxicity; however, the ACD does not recognize the full extent of the morbidity and mortality associated with AAV and the substantial impact this has on patients' quality of life. Therefore, it does not take into account the likely long-term benefits of sustained disease remission and reduced corticosteroid toxicity of an avacopan-based regimen. As outlined in the original company submission, AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patient morbidity, mortality, and quality of life (QoL). Despite current standard of care (SoC) treatment, the mortality rate in GPA and MPA patients remains higher than that of the general population. Longer-term mortality in AAV is increased because of disease-related complications, development of cardiovascular (CV) disease, renal disease, and corticosteroid-related toxicity. In addition, in current management pathways, the risk of corticosteroid-mediated morbidity is likely to increase with each occurrence of relapse. The ACD included comments from one NICE clinical expert stating that infection and cardiovascular disease, which are the most common causes of death in this population, are both associated with corticosteroid use. However, within the ACD the committee does not explicitly recognise how the benefits of reduced corticosteroid usage associated with an avacopan-based regimen will address this current unmet need in AAV and the likely long-term benefits.

Please return to: **NICE DOCS**

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	The ACD also underappreciates the impact of AAV on patients' quality of life. The original company submission highlighted how the chronic relapsing and remitting nature of AAV, requirement for prolonged treatment and corticosteroid-related adverse events, significantly impacts patients' physical and emotional well-being, reducing their quality of life. Despite this, the ACD only references patient and clinical experts commenting on the side effects and toxicity of corticosteroids with regards to improvements in quality of life, and not the quality-of-life improvements associated with sustained disease remission. To our knowledge, ADVOCATE is the only study in AAV that has demonstrated a positive impact of a treatment on patient quality of life. In summary, an avacopan-based regimen provides an effective and needed treatment option for the management of MPA and GPA over the current SoC, as demonstrated by reduction in relapses, statistically significant increase in sustained remission rates, reduced corticosteroid usage and associated adverse events, improvement of renal function, and improvement in patients' QoL.
4	The company agree with the committee recommendation in Section 3.10 that the ERG scenario overestimated the proportion of patients who are expected to receive rituximab maintenance in clinical practice. The company have submitted a revised version of the model which includes results based on an assumption that 35% of patients with previous rituximab induction treatment are eligible for rituximab maintenance treatment (midpoint of the 30%-40% estimated by clinical experts, with 30% and 40% values applied in separate scenario analyses). This analysis is based on a weighted average of model results for the patient subgroup eligible for rituximab maintenance treatment (22.7% of ADVOCATE trial population) and those not eligible (77.3%). The inputs and results of this analysis have been included in the 'RTX maintenance analysis' tab of the updated model file.
5	Section 3.10 – "The ERG commented that the rituximab maintenance scenario was uncertain. It suggested that the company explore additional evidence, for example, observational data. The company did not provide this" Company response for request of additional data from the ERG to inform the analysis of rituximab maintenance: whilst there are a small number of patients in the avacopan compassionate use programme who received maintenance treatment with rituximab, there is no additional real-world evidence which could robustly inform a direct or indirect comparison which includes rituximab maintenance treatment.
6	Section 3.11 – "[The committee] concluded that it was relevant to consider scenarios using the Gercik et al. and Brix et al. hazard ratios, both individually and pooled" The company agree with the committee recommendation that hazard ratio estimates for end stage renal disease from Gercik et al. and Brix et al. need to be considered both separately, and as a pooled estimate, due to the uncertainties involved with the pooling method. In the revised cost-effectiveness model, the company have set the pooled hazard ratio estimated by the ERG (0.947) as the base case, and presented results based on Gercik et al. and Brix et al. individually in order to characterise the impact of uncertainty around this parameter value. The company consider the pooled method to be a conservative base case, give evidence from other studies (e.g. Gopaluni et al. Arthritis Rheumatol 2019;71(5):784-91) which suggest that the true value of the hazard ratio is lower than 0.947.
7	Section 3.12: "The committee concluded that the ERG's approach to hospitalisation costs was more reflective of costs in the NHS in England" The company are concerned that the estimates of hospital cost based on NHS Reference Costs 2019/20 are likely to underestimate the true cost of hospital treatment for patients with AAV in

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	England, for the following reasons: (i) the unit cost in NHS Reference Costs represents an average across all recorded spells linked to the specific healthcare resource group (HRG), and therefore it is not reflective of the cost of long hospital spells, such as the ones observed in the ADVOCATE trial; ii) the average length of stay in the NHS Reference Costs is reflective of the overall patient population with AAV, rather than the more narrowly defined target population with severe, active AAV, and therefore is likely to be an underestimate. The estimates based on NHS Reference Costs 2019/20 without adjustment for excess bed days were applied in the revised company model and should therefore be treated as conservative.
8	Based on the changes outlined above, the base case incremental cost-effectiveness ratio (ICER) in the company model was updated from £19,441 per quality-adjusted life-year gained to £46,465, which is consistent with the NICE committee conclusion that the most plausible ICER would likely be above the ERG's base case ICER of £40,516. To facilitate access to avacopan for the full population covered by its marketing authorisation, the company is seeking to amend the commercial arrangement in place with NHSE which updates the price of avacopan from £'commercial in confidence information removed' to £'commercial in confidence information removed' per 10mg capsule. The new company base case ICER with the updated price is £27,091. In scenarios which assumed that 30% and 40% of rituximab-induced patients are eligible for rituximab maintenance treatment, the ICER was £26,383 and £27,812, respectively. In the scenarios which assumed the HR for end stage renal disease based on Gercik et al. and Brix et al., the ICER was £14,668 and £31,880, respectively.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Vasculitis UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for the opportunity to consult on the appraisal of 'Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis'. We were disappointed to learn that that the appraisal committee's current position is not to recommend the use of avacopan because of the uncertainty in the cost-effectiveness model. We hope that the committee will reconsider their recommendation, not to entertain patient's want but the patient's unmet need for effective treatment.
2	There are three medications available to treat severe GPA and MPA vasculitis, cyclophosphamide, rituximab and corticosteroids. The most effective initial treatment is either a combination of cyclophosphamide and corticosteroids or rituximab and corticosteroids (starting from a high dose, therefore the toxicity is high). **There is an unmet need for new medication to:** **A/ decrease the cumulative toxicity of the medication the patients receive**. From the ADVOCATE trial we know that avacopan group had lower mean Corticosteroid Toxicity Index Cumulative Score (39.7) than the prednisone group (56.6). Side effects from steroid use translate into increase cost for NHS to treat the side effects and related morbidities. Patients must be treated for cataracts in much younger age, many get diagnosed with diabetes, osteoporosis that causes early degeneration of the spine or the hips, mental health issues and the list is endless. My consultant told me that the prolonged time I was on steroids has made my body age by 20 years. At the age of 53 I must have monthly consultations at the pain clinic for the pain caused by the generation of my spine, I have to be seen annually by an ophthalmologist (instead of seeing a private optometrist every two years), I will have to have cataract operations in both eyes in the next couple of years, I have had scans and an MRI plus many consultations in the rheumatology/orthopaedic combined clinic to find the cause of my ongoing pain that made me housebound for quite long time. Here are some comments vasculitis patients have made about the side effects from steroids: [redacted] *: I had a massive bleed was rushed into hospital, they didn't know if I would make it, had to have a blood transfusion, and was taken off them (steroids) straight away.* [redacted]*: When you mention that you've been prescribed steroids people automatically think of the swollen face, tummy and back. The extra weight suddenly appearing. When the skin is so fragile both arms and legs are covered in bruising and scars as well as presenting with muscle wastage. I would like to bring attention to how my mental health has been impacted from taking Prednisone for the past twelve years. The emotional changes I've experienced have been dramatic. My mental well-being has been severely compromised through mood swings, aggression, changes to my personality and appearance. My self esteem and, in turn, self confidence plummeted when people didn't recognise me due to the changes. One of my biggest health challenges currently is steroid-induced diabetes which is currently not controlled. Again all of this impacts how I see myself and how others view me. Without sounding dramatic, steroids almost cost me my family. The enormous changes were difficult for my husband and children to understand or accept. It was only after being prescribed*

Please return to: **NICE DOCS**

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	quetiapine and sertraline that the family unit became more settled. [redacted] *I was suicidal on 30mg, manic on 10mg. Reflux, glaucoma, cataracts, vertebral fractures,insomnia, weight gain, impaired judgement, musculoskeletal problems: all confirmed in clinic…* **B/ to get in remission and sustain it for longer time.** Getting in remission as fast as possible and sustain remission is very important for two reasons. It lessens the risk of organ damage caused by active vasculitis and by remaining in remission the patient doesn't have to go through the initial treatment again followed by maintenance treatment (it can be a vicious cycle: initial treatment, get in clinical remission, maintenance treatment, relapse, initial treatment…) Sustaining remission makes the treatment more cost effective as it decreases the cost of treating the patient again with the initial treatment, the cost of closely monitoring the patient and of course decreases the need of treating side effects caused by high toxicity treatment. During the pandemic we have noticed that many of our members were advised either to postpone or change treatment f they were on Rituximab maintenance treatment because of the increased risk of getting covid and get severely ill. These patients would benefit a lot of sustaining remission and decrease the risk of needing high dose of Rituximab to get in clinical remission again. The committee has noted that clinical trial shows, that after a year, avacopan is more effective at stopping the condition getting worse than standard care (corticosteroids) and that at the week 52, 71.0% of the avacopan group had sustained remission compared to 56.1% of the prednisone group. The difference was even larger at the anti-MPO positive subgroup in which 70.2% of the avacopan group had sustained remission compared to 48.0% in the prednisone group. There are patients with refractory vasculitis that cannot take steroids as they react badly to them, for these patient avacopan could be the chance to get in remission, have a better quality of life and decrease the risk of loosing their life because of vasculitis. [redacted]*: In the past I have been prescribed prednisone to alleviate the following symptoms when my vasculitis was flaring; purpuric rash on legs, swelling, pain, generally feeling unwell and flu like symptoms. The medication did not help alleviate my symptoms but made them worse. I also had a steroid injection prior to my wedding day as I was flaring. Again, it exacerbated my flare.* [redacted]*: Prednisolone has caused me so many problems that I can't wait for an alternative drug. Even with half the side effects it would be so much better. Most of all I want a drug that gives me a break from the constant drain of inflammation, pain and fatigue that goes with my vasculitis, without major side effects. Avacopan seems to promise this, which is why I signed up for the trial. My experience of the trial was not at all good, but I still want that drug!!* [redacted] *I took prednisolone initially to control my GPA symptoms and have managed to taper off steroids, my understanding is it is not appropriate to take steroids long term due to the significant side effects.* *Avacopan is recommended as it is a specific drug which has been developed to control vasculitis symptoms. I was informed by my consultant that there are currently no major side effect from this drug when compared to other drugs which are available. The effect of being able to take avacopan would be that my GPA is adequately controlled along with rituximab infusions. The other drugs which could be used have more side effects and not as effective.*
3	Vasculitis is a life changing illness, and it can be life threatening. Treatment doesn't only alleviate severe symptoms, but also aims to save the life of patients. The cost of treatment is not only the financial cost for NHS, but also, they price patients pay being on toxic medication and the increased cost for NHS to treat the side effects of that treatment. Patients need to have an alternative

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	medication that will put them in remission, but at the same time will not decrease their quality of life. As a GPA patient with lung and sinuses involvement that was severely ill at the time of diagnosis, I am grateful that the medication given to me saved my life, but I wish there was an alternative (like avacopan) that I could have taken. I was diagnosed when I was 45 years old (almost 8 years ago) much younger than the average GPA patient, but I feel like I am 70 most of the time. When I was diagnosed and asked for my prognosis, I was told by my doctor that *I will save you if I don't kill you with the medication I will give you.*
4	For all the reasons above we hope you will reconsider and give the option of a novel treatment to patient with severe GPA or MPA vasculitis.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are disappointed that the appraisal committee is not recommending the use of avacopan with cyclophosphamide or rituximab. Further consideration is needed to ensure more patients can access this treatment, as the effective treatment of patients with severe AAV remains an unmet clinical need, The following key issues highlight the need for this treatment: • **Reduced use of corticosteroids**: There are obvious benefits to a treatment that reduces the cumulative corticosteroid dose. It reduces the side effects and associated morbidity for patients, while also reducing the costs on trust for treating those side effects. Additionally, relapse and the resulting high-dose of corticosteroids for remission induction and increased rituximab exposure is associated with greater NHS activity and spent resources. • **Increased remission**: Rates of remission increased in the avacopan arm of ADVOCATE RCT. • **Benefits to patients**: Certain subgroups of patients benefitted, such as those with relapsed or refractory disease. It is not clear why patients who are MPO positive have benefitted clinically more that those patients who were PR3 positive. • **COVID-19 vaccine effectiveness**: There is an increased risk of non-response to COVID-19 vaccination and worse outcomes for infected patients with high dose corticosteroids and exposure to rituximab
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UKIVAS (United Kingdom and Ireland Vasculitis Society)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** One reason for NICE rejection is that there is no/limited data for maintenance avacopan treatment – we agree there are no data beyond 12 months and NICE could limit approval to 12 months from flare, although for occasional difficult to control patients it will be unfortunate to stop avacopan if it is the only drug that has worked well.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The cost effectiveness model underestimated the risk of kidney failure because it used CPRD data, in which microscopic polyangiitis (MPA) is under-represented and the CPRD population misses the most severe patients, who die/go onto dialysis early and are not necessarily picked up. Data from clinical trials point to a higher kidney failure risk. Additional modelling should examine benefits of avacopan in patients with diabetes and those who are obese, where steroid-sparing is more important.
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** In general, the vasculitis community have accepted the results of the ADVOCATE trials and are keen to bring these advantages to their patient population, in whom drug choice remains quite limited and toxicity high. There is a subgroup of patients with refractory ANCA vasculitis who have the highest risk for death and kidney failure, in whom an alternative therapy is needed.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

Consultation on the appraisal consultation document – deadline for comments **5pm on 17 June 2022**. Please submit via NICE Docs.

send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis [ID1581]

ERG RESPONSE TO COMPANY COMMENTS ON THE APPRAISAL CONSULTATION DOCUMENT

Comment number	Comments	ERG response
1	Section 2.1 - Marketing authorisation indication We request that the committee's recommendation should take into consideration that the MRHA has granted avacopan (Travneos) marketing authorisation with orphan status. In qualifying for orphan designation the MHRA have acknowledged the following: • Severe and active GPA and MPA is a chronically debilitating, life threatening disease. • The number of patients with severe active GPA and MPA eligible for an avacopan-based regimen in England each year (n=1,346) is significantly less than the orphan drug threshold of 5 in 10,000. • Avacopan is of significant benefit to those affected by severe active GPA or MPA	The ERG acknowledges that the MRHA has granted avacopan marketing authorisation with orphan status.
2	Section 2.3 – Price The list price for avacopan (Tavneos) has been approved by DHSC, therefore it is no longer confidential. The list price for avacopan (Tavneos) is £5,547.95 for a 180 pack of 10mg capsules.	The ERG acknowledges that the list price is now no longer confidential.
3	Section 3.1 – "The committee recognised that people with severe active GPA or MPA can have severe symptoms" Section 3.2 – "The committee concluded that people with GPA or MPA, and clinicians, would welcome a new treatment option that could reduce the need for corticosteroids" Section 3.6 – "The committee concluded that avacopan was effective at sustaining disease remission and reducing corticosteroid-induced toxicity compared with a prednisone-based regimen in the intention-to-treat population of ADVOCATE" We agree that patients with GPA and MPA can have severe symptoms and that avacopan is effective at sustaining disease remission and reducing corticosteroid toxicity; however, the ACD does not recognize the full extent of the morbidity and mortality associated with AAV and the substantial impact this has on patients' quality of life.	The ERG has no comments

	Therefore, it does not take into account the likely long-term benefits of sustained disease remission and reduced corticosteroid toxicity of an avacopan-based regimen. As outlined in the original company submission, AAV is a rare, potentially fatal, remitting-relapsing, autoimmune condition that has a substantial impact on patient morbidity, mortality, and quality of life (QoL). Despite current standard of care (SoC) treatment, the mortality rate in GPA and MPA patients remains higher than that of the general population. Longer-term mortality in AAV is increased because of disease-related complications, development of cardiovascular (CV) disease, renal disease, and corticosteroid-related toxicity. In addition, in current management pathways, the risk of corticosteroid-mediated morbidity is likely to increase with each occurrence of relapse. The ACD included comments from one NICE clinical expert stating that infection and cardiovascular disease, which are the most common causes of death in this population, are both associated with corticosteroid use. However, within the ACD the committee does not explicitly recognise how the benefits of reduced corticosteroid usage associated with an avacopan-based regimen will address this current unmet need in AAV and the likely long-term benefits. The ACD also underappreciates the impact of AAV on patients' quality of life. The original company submission highlighted how the chronic relapsing and remitting nature of AAV, requirement for prolonged treatment and corticosteroid-related adverse events, significantly impacts patients' physical and emotional well-being, reducing their quality of life. Despite this, the ACD only references patient and clinical experts commenting on the side effects and toxicity of corticosteroids with regards to improvements in quality of life, and not the quality-of-life improvements associated with sustained disease remission. To our knowledge, ADVOCATE is the only study in AAV that has demonstrated a positive impact of a treatment on patient quality of life. In summary, an avacopan-based regimen provides an effective and needed treatment option for the management of MPA and GPA over the current SoC, as demonstrated by reduction in relapses, statistically significant increase in sustained remission rates, reduced corticosteroid usage and associated adverse events, improvement of renal function, and improvement in patients' QoL.	
4	The company agree with the committee recommendation in Section 3.10 that the ERG scenario overestimated the proportion of patients who are expected to receive rituximab maintenance in clinical practice. The company have submitted a revised version of the	The ERG indeed presented scenarios where all patients who had received rituximab during induction would receive rituximab

	model which includes results based on an assumption that 35% of patients with previous rituximab induction treatment are eligible for rituximab maintenance treatment (midpoint of the 30%-40% estimated by clinical experts, with 30% and 40% values applied in separate scenario analyses). This analysis is based on a weighted average of model results for the patient subgroup eligible for rituximab maintenance treatment (22.7% of ADVOCATE trial population) and those not eligible (77.3%). The inputs and results of this analysis have been included in the 'RTX maintenance analysis' tab of the updated model file.	during maintenance as well, in line with the request the ERG received from the NICE technical team. It is useful that the company now presents an analysis that is based on real life UK maintenance therapy for AAV patients The ERG has checked the model implementation of this and has not found any issues.
5	Section 3.10 – "The ERG commented that the rituximab maintenance scenario was uncertain. It suggested that the company explore additional evidence, for example, observational data. The company did not provide this" Company response for request of additional data from the ERG to inform the analysis of rituximab maintenance: whilst there are a small number of patients in the avacopan compassionate use programme who received maintenance treatment with rituximab, there is no additional real-world evidence which could robustly inform a direct or indirect comparison which includes rituximab maintenance treatment.	In the key issue summary, the ERG indeed indicated that due to lack of data from RCTs to enable an NMA to inform the analysis of rituximab maintenance, there might be observational data available for that purpose. Of course, if the company has made a concerted effort to find such data but remained unsuccessful, then the current naïve approach is a pragmatic alternative.
6	Section 3.11 – "[The committee] concluded that it was relevant to consider scenarios using the Gercik et al. and Brix et al. hazard ratios, both individually and pooled" The company agree with the committee recommendation that hazard ratio estimates for end stage renal disease from Gercik et al. and Brix et al. need to be considered both separately, and as a pooled estimate, due to the uncertainties involved with the pooling method. In the revised cost-effectiveness model, the company have set the pooled hazard ratio estimated by the ERG (0.947) as the base case, and presented results based on Gercik et al. and Brix et al. individually in order to characterise the impact of uncertainty around this parameter value. The company consider the pooled method to be a conservative base case, give evidence from other studies (e.g. Gopaluni et al. Arthritis Rheumatol 2019;71(5):784-91) which suggest that the true value of the hazard ratio is lower than 0.947.	The ERG acknowledges that the company base case is now based on the pooled hazard ratio, using Gerick et al. and Brix et al.
7	Section 3.12: "The committee concluded that the ERG's approach to hospitalisation costs was more reflective of costs in the NHS in England"	The ERG concurs with the company's approach to use the NHS Reference Costs 2019/20 without adjustments to reflect hospitalisation costs for AAV.

	The company are concerned that the estimates of hospital cost based on NHS Reference Costs 2019/20 are likely to underestimate the true cost of hospital treatment for patients with AAV in England, for the following reasons: (i) the unit cost in NHS Reference Costs represents an average across all recorded spells linked to the specific healthcare resource group (HRG), and therefore it is not reflective of the cost of long hospital spells, such as the ones observed in the ADVOCATE trial; ii) the average length of stay in the NHS Reference Costs is reflective of the overall patient population with AAV, rather than the more narrowly defined target population with severe, active AAV, and therefore is likely to be an underestimate. The estimates based on NHS Reference Costs 2019/20 without adjustment for excess bed days were applied in the revised company model and should therefore be treated as conservative.	The ERG also recognises that these cost estimates might be conservative, though this is difficult to judge with certainty. A better understanding of the length of hospitalisation could be found through a study of patient records of AAV patients within the licensed indication who have been hospitalised in e.g. the last 2 years. A note should be made that in checking the company's updated model, the ERG found that they (the ERG) had made an error in calculating the mean cost per day. The correct value, used by the company, is £2,758 per stay, whereas the ERG has used the value of £2,849 in earlier calculations. The impact on the ICER is negligible.
8	Based on the changes outlined above, the base case incremental cost-effectiveness ratio (ICER) in the company model was updated from £19,441 per quality-adjusted life-year gained to £46,465, which is consistent with the NICE committee conclusion that the most plausible ICER would likely be above the ERG's base case ICER of £40,516. To facilitate access to avacopan for the full population covered by its marketing authorisation, the company is seeking to amend the commercial arrangement in place with NHSE which updates the price of avacopan from £[redacted] to £[redacted] per 10mg capsule. The new company base case ICER with the updated price is £27,091. In scenarios which assumed that 30% and 40% of rituximab-induced patients are eligible for rituximab maintenance treatment, the ICER was £26,383 and £27,812, respectively. In the scenarios which assumed the HR for end stage renal disease based on Gercik et al. and Brix et al., the ICER was £14,668 and £31,880, respectively.	The ERG has checked all analyses and found no issues. The current company base case includes all assumptions/estimates from the previous ERG preferred base case, as well as the addition of the assumption that 35% of patients receiving rituximab during induction therapy also receive it as maintenance. As that latter assumption reflects clinical practice in the UK, according to the clinical experts in the first Appraisal Committee Meeting, the ERG agrees with including this in the base case. Hence, the ERG preferred base case is the currently provided company base case. To assess rituximab as maintenance therapy, the HR of relapse-free survival for rituximab versus azathioprine was applied to the relapse rates observed during maintenance therapy in the ADVOCATE study. That HR was estimated to be 0.36, with a 95% CI of 0.23-0.57. The ERG ran exploratory analyses using the boundaries of this confidence interval, yielding an ICER of £28,416 with a HR of 0.23 and of £25,253 with a HR of 0.57.