National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Avacopan for treating anti-neutrophil cytoplasmic autoantibody-associated vasculitis [ID1581]

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 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Vifor Pharma	We agree that given the potential for avacopan to address the unmet medical needs around sustaining remission and reducing morbidity and mortality associated with both the condition itself and the current standard care, it is entirely appropriate to refer this topic to NICE for a single technology appraisal	Thank you, your comment has been noted. No changes have been made.
	British Society for Rheumatology	Some patients with AAV do not respond to current therapies used for induction and maintenance or are unable to tolerate the current therapies so another option is welcome and helps to address an unmet need for these patients who can experience severe organ threatening disease and death	Thank you, your comment has been noted. No changes have been made.
Wording	Vifor Pharma	Suggest replacing the word ‘antibody’ with ‘autoantibody’	Comment noted. The scope has been amended to refer to autoantibody-associated vasculitis.

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Timing Issues	Vifor Pharma	The timely referral of this topic will enable patients and the NHS to benefit from appraisal guidance at the anticipated time of UK launch of avacopan in 2022.	Comment noted. No changes needed.
	British Society for Rheumatology	Despite current available therapies patients may not achieve remission or can experience recurrent flares and toxicities secondary to available therapies including hypogammaglobulinaemia with rituximab, malignancy with multiple courses of IV cyclophosphamide, infertility, and an early menopause also with cyclophosphamide and toxicity due to glucocorticoids including diabetes mellitus, osteoporosis, hypertension, obesity, cataracts.	Thank you, your comment has been noted. No changes have been made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Vifor Pharma	We suggest some edits would be useful to set the scene for the appraisal of this drug which is targeted for this rare disease. The underlying mechanisms in ANCA-associated vasculitis are more clearly described and the acute vasculitic process is due to uncontrolled activity of the innate immune system (Jeanette and Nachman 2017). Following loss of tolerance and development of the ANCA autoantibody, at a later time primed neutrophils interact with ANCA and are activated. Activated neutrophils release mediators which accelerate the alternative complement system and its terminal effector protein C5a attracts more neutrophils, stimulates their adhesion to small blood vessel walls and release of contents in an inflammatory amplification loop leading to necrotic damage. We suggest an edit of the disease description to capture the current view of disease mechanisms – ANCA-associated vasculitis has a complex pathophysiology beginning with the generation of ANCA	Thank you for your comments. The background section is intended to provide a brief summary of the disease. This section has been amended to include data from Pearce (2017) and to further clarify the aim of treatment.

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		autoantibodies. The small vessel vasculitis is driven by the interaction of neutrophils and the activated alternative complement system which leads to tissue inflammation and damage. We suggest an edit of the summary of incidence and prevalence in the UK to ensure clarity. The incidence of GPA is estimated to be 11 per million population and the incidence of MPA is estimated to be 6 per million population (BSR and BHPR guidance reference 4). A recent CPRD and HES based study (Pearce 2017) has estimated the incidence of GPA only as 11.8 per million population and a prevalence of 134.9 per million population. This study also demonstrated no differences in the BAME population. We suggest additional clarity around the disease natural history and therapy goals since these are not based on disease progression. ANCA associated vasculitis is a relapsing remitting long term condition and the BSR and BHPR guidance (reference 4) stresses that therapy is aimed at rapidly inducing remission and sustaining it, thereby preventing organ damage while also avoiding drug toxicity.	
The technology/ intervention	Vifor Pharma	Avacopan is a selective complement 5a (C5a) receptor antagonist (C5aR1). We suggest an edit to demonstrate the fact that Avacopan is an alternative to, rather than an add-on to standard care. Avacopan has been studied in Phase 2 and 3 clinical trials as an alternative to glucocorticoids (e.g. prednisone). In the current treatment paradigm GCs are used in the treatment of ANCA associated vasculitis, initially at high dose with cyclophosphamide or rituximab and then often prolonged lower dose GC is used with rituximab or azathioprine/mycophenolate. The ADVOCATE pivotal Phase 3 trial compared avacopan to a standard glucocorticoid regime in achieving and sustaining remission. Patients also received immunosuppression as above.	Thank you for your comments. The phrase “add-on” has been removed from the intervention description in the table, The wording in the technology section aims to be broad to cover all relevant trials of avacopan. The wording has been amended to refer to immunosuppressive and corticosteroid treatments that

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			could be used as part of standard care. The outcomes section also includes use of corticosteroid and this could include corticosteroid sparing.
Population	Vifor Pharma	The population has been defined appropriately. There are no groups within this population which warrant separate consideration.	Comment noted. No changes needed.
Comparators	Vifor Pharma	[redacted] The Phase 3 clinical trial ADVOCATE in patients with active organ or life threatening ANCA associated vasculitis demonstrated that avacopan is an alternative to glucocorticoids (prednisone) in treating ANCA associated vasculitis in regimes along with either cyclophosphamide followed by azathioprine/mycophenolate mofetil or rituximab. The standard glucocorticoid regimen involves a high dose tapering as remission is achieved but often then continued at low dose to sustain remission. Methotrexate and mycophenolate mofetil are recommended as alternatives to cyclophosphamide / azathioprine or rituximab for remission induction in patients with localised disease at low risk of suffering organ damage. These patients were not studied in ADVOCATE and so, in this setting, they are not relevant comparators for avacopan. Proposed wording:- Established treatment regimens without avacopan, including glucocorticoids in combination with either cyclophosphamide (followed by, azathioprine / mycophenolate), or rituximab.	Thank you for your comments. The list of comparators is broad and aims to capture all possible treatments that may be used in clinical practice. During the development of the technology appraisal, the appraisal committee will consider which comparator is most appropriate. No changes have been made.

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	British Society for Rheumatology	A combination of IV cyclophosphamide and rituximab as well as monotherapy with either agent; there appears to be some synergy when a combination is used. However some patients are not given cyclophosphamide if there is a fertility concern, already received a high cumulative dose of cyclophosphamide. All patients will currently receive some glucocorticoids and the aim is to reduce them as quickly as possible; the rate of reduction is governed by the clinical response.	Comment noted. The current wording allows for possible treatment with cyclophosphamide and rituximab as well as monotherapy with either. No changes have been made.
Outcomes	Vifor Pharma	We agree that the identified outcome measures are largely complete but since avacopan is a targeted therapy to reduce/replace glucocorticoids and avoid associated serious toxicity we would wish to add; • Glucocorticoid toxicity (measured with an objective score) • Glucocorticoid related adverse events • Sustained glucocorticoid free vasculitis remission. Since infection is such a clinical challenge in ANCA associated vasculitis we suggest that risk of infection is examined separately from overall adverse events.	Thank you for your comments. The list of outcomes are examples and not intended to be an exhaustive list. It is anticipated that glucocorticoid toxicity and adverse events would be captured as part of the broader outcome 'use of immunosuppressants and corticosteroids'. Corticosteroid toxicity has been added as an example.
	British Society for Rheumatology	Steroid sparing effect is particularly important Reduction in glucocorticoid toxicity	Thank you for your comments. The list of outcomes are examples and not intended to be an exhaustive list. It is anticipated that glucocorticoid toxicity and sparing effect would be captured as part of the broader outcome 'use of

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			immunosuppressants and corticosteroids'. Corticosteroid toxicity has been added as an example.
Economic analysis	Vifor Pharma	ANCA-associated vasculitis is a serious, life-threatening long term condition for which there is no cure. Patients are at risk from high short term and long term mortality as well as cumulative organ damage from vasculitis activity and glucocorticoid related toxicity. Therefore a cost-utility model with a life-time horizon may be required for all cost and outcomes associated with treatment to be captured in the analyses. Cost comparison methodology would not be appropriate for this topic.	Comment noted. No changes needed.
	British Society for Rheumatology	Avacopan may be more cost-effective in patients with severe organ involvement and those who have developed complications from standard therapy, resistant to standard therapy or unable to tolerate standard therapy.	Comment noted. The use of subgroups will be explored by the committee during the development of the appraisal. This will depend on the availability of evidence. No changes needed.
Equality and Diversity	Vifor Pharma	Vifor Pharma are not aware of any issues of inequality or discrimination arising from the proposed scope.	Comment noted. No changes needed.
Innovation	Vifor Pharma	Avacopan is a novel, first in class, highly selective C5aR1 antagonist. By blocking the receptor for the pro-inflammatory complement system terminal product C5a, avacopan prevents attraction and further activation of destructive inflammatory cells such as neutrophils which migrate through small vessels and cause tissue damage. Avacopan specifically blocks the amplification of this inflammatory interaction	Comment noted. The committee will consider the extent to which avacopan is innovative during the development of the appraisal. No changes needed.

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		between C5a and neutrophils which is the driver of organ damage in ANCA-associated vasculitis. Current standard treatments for ANCA-associated vasculitis consist of regimens which rely on glucocorticoids (high dose and then prolonged lower dose) and immunosuppression and are associated with challenges in achieving sustained remission along with increased risks of infection, significant glucocorticoid related toxicity and cumulative organ damage including progressive renal failure. Avacopan in comparison to glucocorticoids results in superior sustained remission at 52 weeks, significant reduction in glucocorticoid-related toxicity, significant improvement in kidney function in patients with renal disease as well as improved Quality of Life and, therefore, has the potential to fundamentally change the treatment paradigm of patients with ANCA-associated vasculitis. The patient experience in ANCA-associated vasculitis is very challenging and avacopan has the potential to improve patient quality of life and functional status.	
	British Society for Rheumatology	Yes it is innovative and potentially step changing as it is corticosteroid sparing It is also oral so reduces the number of hospital attendances which is particularly pertinent during the COVID-19 pandemic.	Comment noted. The committee will consider the extent to which avacopan is innovative during the development of the appraisal. No changes needed.
NICE Pathways	Vifor Pharma	As a treatment for vasculitis, it would be appropriate to capture avacopan within the 'Systemic connective tissue conditions' section of the existing NICE pathway.	Comment noted. No changes needed.

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Additional comments on the draft scope	Vifor Pharma	Rituximab is now indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).	Thank you for your comment. The comparators section has been updated to reflect this.
	British Society for Rheumatology	The specialised rheumatology clinical reference group should be added to the stakeholder list	Comment noted. This group has been added to the stakeholder list.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

References

Jennette J.C and Nachman P.H. ANCA Glomerulonephritis and Vasculitis. Clin J Am Soc Nephrol 2017; 12: 1680–1691

Pearce F.A et al. The incidence, prevalence and mortality of granulomatosis with polyangiitis in the UK Clinical Practice Research Datalink. Rheumatology 2017; 56: 589-596