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

Slides for public observers

Technology appraisal committee D, 7 July 2022

Chair: Megan John

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Catie Parker, Lorna Dunning, Linda Landells

Company: Vifor Pharma

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Recommendation from first meeting

Avacopan with a cyclophosphamide or rituximab regimen is not recommended, within its marketing authorisation, for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults.

Why the committee made these recommendations

- It was concerned that the modelled maintenance treatment did not reflect NHS practice
- There was uncertainty about the representativeness of healthcare costs
- There was uncertainty about the most appropriate estimate of the hazard ratio for end-stage renal disease per unit change in estimated glomerular filtration rate
- It considered the most plausible ICER was above the range normally considered cost effective

Abbreviations: ICER, incremental cost-effectiveness ratio

Avacopan (Tavneos, Vifor Pharma)

Table 1 Technology details

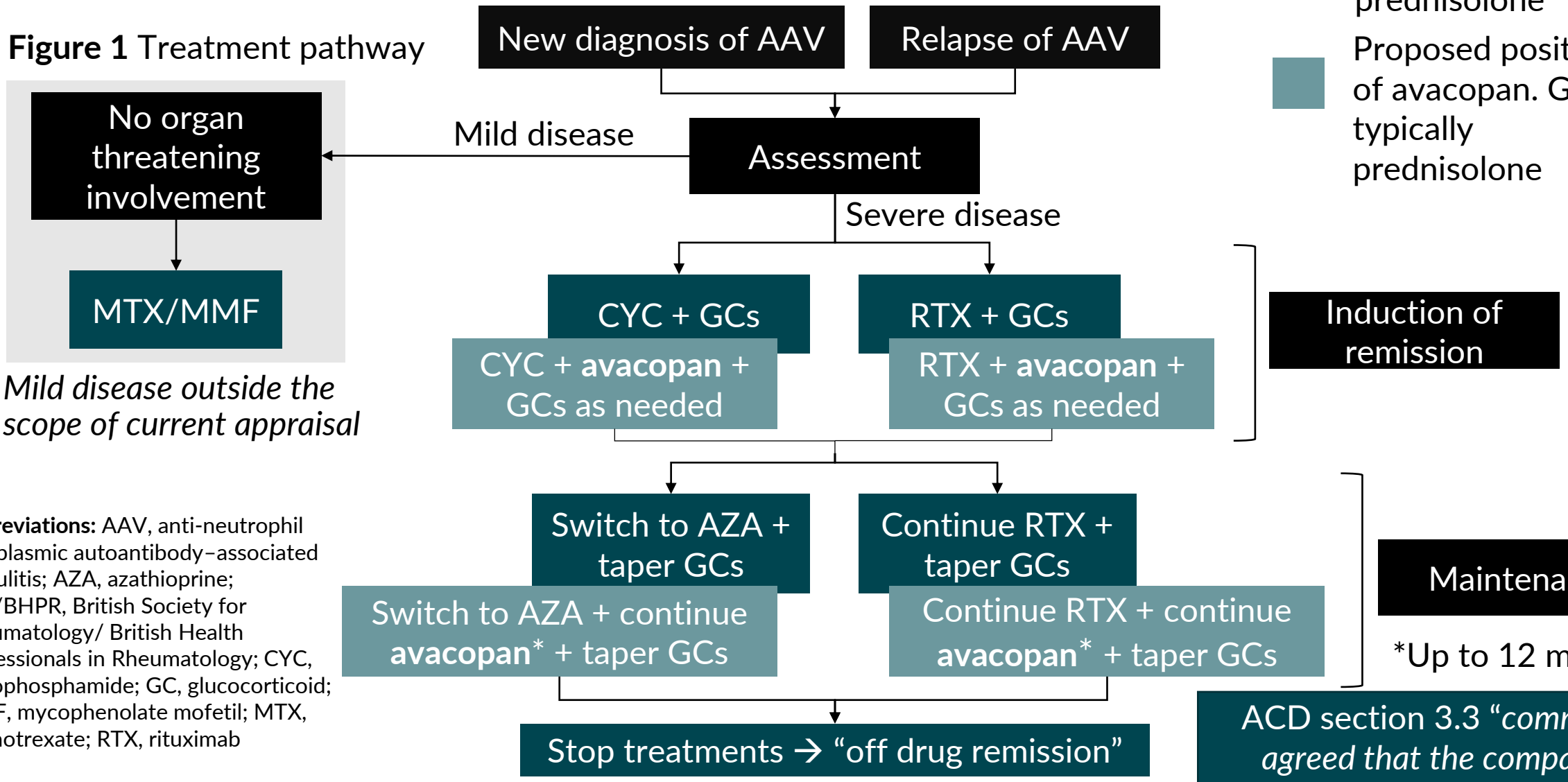
Marketing authorisation	• Avacopan, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) • Granted by MHRA; May 2022
Mechanism of action	Highly selective C5aR1 antagonist
Administration	3 x 10 mg capsules taken orally twice per day with food
Price	• List price per pack of 180 capsules: £5,547.95 • Annual cost of treatment: approximately £67,311 • PAS price available – updated discount after first meeting

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency

Treatment pathway

Avacopan is proposed as an add-on to current care

Figure 1 Treatment pathway



Mild disease outside the scope of current appraisal

Current treatment option. GC, typically prednisolone

Proposed position of avacopan. GC, typically prednisolone

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; AZA, azathioprine; BSR/BHPR, British Society for Rheumatology/ British Health Professionals in Rheumatology; CYC, cyclophosphamide; GC, glucocorticoid; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab

Adapted from BSR/BHPR guideline for the management of adults with ANCA-associated vasculitis

ACD section 3.3 "*committee agreed that the company's positioning was appropriate*"

Clinical effectiveness recap

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Key clinical trial - ADVOCATE

Table 2 Clinical trial design and outcomes

	ADVOCATE
Design	Randomised (1:1), double-blind, active controlled trial
Population	• People with GPA or MPA • Anti-PR3 or anti-MPO antibody positive • At least 1 major item, 3 minor items, or 2 renal items of proteinuria and hematuria in BVAS
Intervention	Avacopan (with CYC then AZA or RTX then nothing)
Comparator	Prednisone (with CYC then AZA or RTX then nothing)
Duration	52 weeks
Primary outcome	Proportion with disease remission at weeks 26 & 52
Key secondary outcomes	• Glucocorticoid induced toxicity • BVAS=0 at week 4 • Change in HRQoL • Proportion with disease relapse
Locations	North America, Europe (including UK), Japan and New Zealand
Used in model?	Yes

ACD sections 3.4 and 3.5 *"relevant induction treatment comparators are CYC or RTX with high-dose corticosteroids… relevant maintenance treatment comparators are AZA or RTX with corticosteroids"*

Trial did not include rituximab maintenance

Abbreviations: AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; HRQoL, health-related quality of life; MPA, microscopic polyangiitis; MPO, Myeloperoxidase; PR3, Proteinase 3; RTX, rituximab

Clinical trial results – ADVOCATE ITT population

ACD section 3.6 "*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*"

Table 3 Clinical trial results for intention to treat population

Outcome	Treatment group	% (n/N) or LSM ± SEM	Estimated common difference (95% CI, p-value) or p-value
Remission at 26 weeks*	Avacopan group	72.3% (120/166)	3.4% (-6.0 to 12.8, p<0.001 for non-inferiority and p=0.24 for superiority)
	Prednisone group	70.1% (115/164)	
Sustained remission at 52 weeks	Avacopan group	65.7% (109/166)	12.5% (2.6 to 22.3, p<0.001 for non-inferiority and p=0.007 for superiority)
	Prednisone group	54.9% (90/164)	
Glucocorticoid-induced toxicity (GTI) cumulative worsening score at 26 weeks	Avacopan group	39.7±3.43	p=0.0002
	Prednisone group	56.6±3.45	

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LSM, least squares mean; n, number of participants; SEM, standard error of measurement

Cost effectiveness recap

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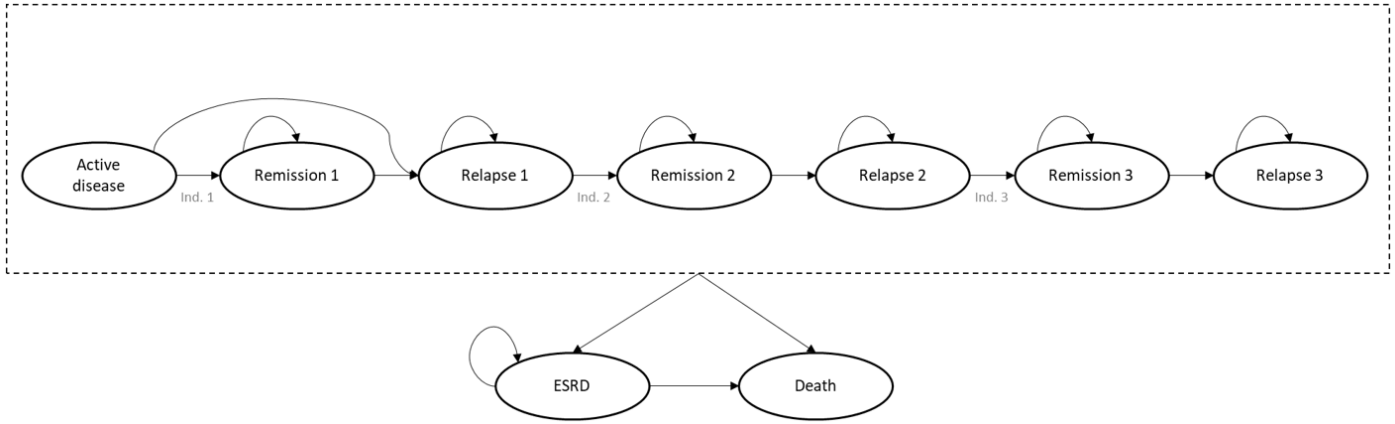
Company's model overview

Figure 3 Model structure



- Technology affects **costs** by:
  - Higher unit price than current treatments
  - Reducing costs for treatment of ESRD
  - Reducing hospitalisation costs
- Technology affects **QALYs** by:
  - Increasing remission rates
  - Decreasing relapse rates
  - Reducing ESRD and associated mortality

Company

- 40 year horizon
- 28-day cycle with half-cycle corrections
- Relapse 1 & 2 each have tunnel states for 6 cycles of induction therapy
- Transitions through model based on disease remission or relapse until ESRD, 3rd relapse or death

ACD section 3.9 "*[the committee] concluded that the company's overall model structure was appropriate for decision making*"

Abbreviations: ESRD, end-stage renal disease; QALY, quality-adjusted life year

Committee preferred assumptions and conclusions

Table 5 Committee preferred assumptions and conclusions from the first meeting

Issue	Committee conclusion
Relevant induction treatment comparators	Rituximab or cyclophosphamide with high-dose corticosteroids
Relevant maintenance treatment comparators	Rituximab (for 30% to 40% of people who had it as induction treatment) or azathioprine
Subgroups	Efficacy varies across prespecified clinical subgroups. Analyses have limitations: • Small sample size • Some more easily identifiable in clinical practice than others • Lack of biological rationale for variation in efficacy
Corticosteroid use in avacopan arm of ADVOCATE	Non-study supplied corticosteroids use in the avacopan arm reflects expected use in clinical practice
ESRD hazard ratio	Considered the Gercik et al. (2020) and Brix et al. (2018) hazard ratios relevant, both individually and pooled, for decision making
Hospitalisation costs	2019/20 NHS reference costs with no adjustment for excess bed days
Representativeness of healthcare costs	Uncertainty around representativeness of modelled healthcare costs

Abbreviations: ESRD, end-stage renal disease

Response to consultation

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ACD consultation responses

- Company (Vifor Pharma)
- 3 Consultees
    - British Society for Rheumatology
    - UK and Ireland Vasculitis Society
    - Vasculitis UK
- No web comments

Abbreviations: ACD, appraisal consultation document

Summary of stakeholder comments

Stakeholders wanted further consideration on the benefits to patients and use of evidence in the model

British Society for Rheumatology

- There is need for this treatment because:
    - It reduces the use of corticosteroids
    - It increases rate of remission
    - Some subgroups had high clinical benefit (relapsed or refractory disease and people with MPO positive disease)
    - COVID-19 vaccine effectiveness

UK and Ireland Vasculitis Society

- Limited data beyond 12 months, so potentially use stopping rule but it may be difficult to implement
- Model underestimated risk of kidney failure because it used CPRD data which may not capture people with most severe disease
- An alternative treatment is needed, especially for refractory disease

Vasculitis UK

- There is unmet need for this medication because:
    - It decreases cumulative toxicity from corticosteroids which can be severe and associated with pain, mood swings, weight gain that impacts self esteem, diabetes, osteoporosis and cataracts
    - It is effective at inducing disease remission which lessens risk of organ damage

Abbreviations: CPRD, Clinical Practice Research Datalink; MPO, Myeloperoxidase

Key issues

Table 6 Key issues

Issue	Resolved?	ICER impact
Rituximab maintenance treatment	Partially – for discussion	Large
Healthcare costs for standard care	Partially – for discussion	Unknown
Hospitalisation costs and excess bed days	Yes	Large
Hazard ratio for end-stage renal disease per unit change in estimated glomerular filtration rate	Yes	Large
Glucocorticoids in the intervention group	Yes	Unknown
Probability of transitioning to end-stage renal disease – calibrated transition probabilities in line with previously published estimates of cumulative incidence of ESRD in AAV (resolved at technical engagement)	Yes	Large

Abbreviations: AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ESRD, end-stage renal disease

Key issue: Rituximab maintenance treatment

The company updated its base case to include rituximab maintenance treatment consistent with committee preference

Background

- In NHS, 30% to 40% of people continue rituximab as maintenance in line with NHS commissioning policy
- Company: no high quality comparative evidence, so old base case excluded rituximab maintenance → only modelled azathioprine maintenance. Provided rituximab maintenance model option, but noted limitations

ACD: committee concluded rituximab maintenance should be included in cost-effectiveness analysis

Company

- New base case assumes 35% of people with previous rituximab induction treatment are eligible for rituximab maintenance treatment → scenarios using 30% and 40%
- No additional real-world evidence available to inform the analysis of rituximab maintenance
- Base case is weighted average of results for people who are (22.7%) and are not (77.3%) eligible for rituximab maintenance from ADVOCATE

ERG comments

- If the company has made a concerted effort to find observational data and there is none, the current naïve approach is practical
- Useful that the company presents analysis reflecting UK practice, and no issues with implementation

Is the company's rituximab maintenance treatment analysis appropriate?

Key issue: Healthcare costs

No new evidence was presented to resolve uncertainty about modelled healthcare costs, but ERG is not too concerned

Background

- There were differences between modelled standard of care healthcare costs and those in the CPRD observational study of resource use for people with GPA or MPA in England
- Also uncertain why the ICER increased when CPRD was used to estimate cost of adverse events

ACD: committee concluded there was uncertainty around representativeness of modelled healthcare costs

Company

- No additional information provided during consultation

ERG comments

- Post ACD modelled healthcare costs for standard care around £15,000 less than reported in CPRD study
- CPRD data unable to be explored further as it includes limited detail on exact resource use and does not include people who had avacopan treatment
- Healthcare costs remain uncertain but unlikely to increase the ICER as:
  - Some of the increased costs would apply to both avacopan and standard care
  - Avacopan may reduce resource use via sustained remission, reduced ESRD and less corticosteroid toxicity

Do the modelled healthcare costs adequately reflect those in the NHS?

Abbreviations: CPRD, Clinical Practise Research Datalink; ESRD, end-stage renal disease; GPA, granulomatosis with polyangiitis; ICER, incremental cost-effectiveness ratio; MPA, microscopic polyangiitis

Resolved: Hazard ratio for end-stage renal disease

The company provided analyses using pooled and individual estimates consistent with committee preference

Background

- In model, probability of ESRD in active and remission states is adjusted based on change in eGFR → company and ERG used different HRs for adjustment and this had large impact on ICER
- Company used Gercik et al. (HR=0.90) because most relevant study and considered it inappropriate to pool estimates from different Cox models because they adjust for different covariates
- ERG preferred to pool estimates from Gercik et al. and Brix et al. (pooled HR=0.95)

ACD: committee considered Gercik et al. and Brix et al. estimates were relevant individually and pooled

Company

- Agree with committee conclusion, base case uses pooled (HR=0.95) and scenarios for individual estimates
- Pooled estimate is likely conservative, Gopaluni et al. suggests HR could be lower

ERG comments

- Acknowledge the company base case is now based on the pooled hazard ratio of Gerick et al. and Brix et al.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; ICER, incremental cost-effectiveness ratio

Resolved: Hospitalisation costs and excess bed days

The company updated its base case to align with committee preference of 2019/20 reference costs and no adjustment for excess bed days

Background

- Company originally used unit costs from 2019/20 NHS reference costs plus excess bed days from 2017/18
- ERG used 2019/20 costs with no adjustment for excess bed days
- NHSE confirmed 2019/20 costs include excess bed days so committee preferred those with no adjustment

ACD: committee concluded the ERG's approach to hospitalisation costs was more reflective of the NHS

Company

- After consultation, use 2019/20 reference costs in base case, but concerned these underestimate true costs:
  - Unit costs represent average and so don't reflect cost of long stays, like those in ADVOCATE
  - Average length of stay in reference costs is overall population with AAV, not narrower population of people with severe, active disease

ERG comments

- Agree with company's updated approach
- A study of AAV patient records within the licensed indication who have been hospitalised recently may be useful

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis

Summary of base case assumptions

The company and ERG base case assumptions are aligned and consistent with committee preferences

Table 7 Committee preferred assumptions and company and ERG base cases

Assumption	Committee preference	Company base case	ERG base case
Rituximab maintenance treatment	30% to 40% who had rituximab induction have it as maintenance treatment	35% who had rituximab as induction have it as maintenance treatment • 30% and 40% scenarios	35% who had rituximab as induction have it as maintenance treatment • added 50% scenario
HR for relapse-free survival for rituximab versus azathioprine	N/A (not discussed at first meeting)	HR=0.36	HR=0.36 • Scenarios using 95% CI boundaries (0.23 and 0.57)
Hospitalisation costs	2019/20 unit costs, no adjustment for excess bed days	2019/20 unit costs, no adjustment for excess bed days	2019/20 unit costs, no adjustment for excess bed days
HR for ESRD per unit change in eGFR	Gercik et al. and Brix et al. estimates are relevant individually and pooled	Pooled estimate (Gercik et al. and Brix et al.) HR=0.95 • Scenarios using individual estimates	Pooled estimate (Gercik et al. and Brix et al.) HR=0.95 • Scenarios using individual estimates

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio

Cost effectiveness results – overview

- Cost-effectiveness results will be presented in part 2 because of confidential comparator discounts
- The company and ERG agree on all assumptions, so they have the same base case ICER
- The base case ICER and most of the scenarios presented by the company and ERG are between £20,000/QALY and £30,000/QALY (not including confidential comparator discounts)
  - 1 below £20,000/QALY
  - 1 above £30,000/QALY

Abbreviations: ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

Other considerations

No comments were received during consultation about equality or innovation

Equality considerations

ACD section 3.16 "*[the committee] concluded that its recommendation for avacopan would not have a different effect on people protected by the equality legislation than on the wider population*"

- No potential equality issues received during consultation on the ACD

Innovation

ACD section 3.17 "*the committee concluded that there may be some benefits of avacopan in terms of reducing future need for rituximab that were not captured in the cost-effectiveness analysis*"

- No comments about innovation received during consultation on the ACD

Abbreviations: ACD, appraisal consultation document

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Thank you.