NCPE Assessment

Technical Summary

Avacopan (Tavneos®)

HTA ID: 22009

20 July 2023

Applicant: Vifor Pharma

Avacopan, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis or microscopic polyangiitis.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of avacopan (Tavneos®)

Following assessment of the Applicant's submission, the NCPE recommends that avacopan (Tavneos®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Vifor Pharma) Health Technology Assessment of avacopan (Tavneos®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In April 2022, Vifor Pharma submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of avacopan (Tavneos®) for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Vifor Pharma is seeking reimbursement of avacopan under the High Tech Drug Arrangement. Avacopan is a first-in-class selective antagonist of the human complement 5a receptor. The dose of avacopan is 10mg (3 hard capsules of 10mg each) taken orally twice daily. Clinical study data are limited to 52 weeks of exposure followed by 8 weeks of observation. The standard of care (SoC) for this group of patients in Ireland is induction treatment with a tapered glucocorticoid regimen used in combination with either rituximab or cyclophosphamide. This is followed by maintenance treatment with glucocorticoids and either rituximab or azathioprine.

1. Comparative effectiveness of avacopan

The efficacy and safety of avacopan was investigated in the ADVOCATE trial, an international 52-week, phase III, randomised, double-blind, double-dummy, active-controlled trial conducted in 331 patients with severe, active GPA or MPA. Participants were randomised on a 1:1 basis to receive add-on treatment with avacopan or an oral tapered prednisolone regimen. Avacopan was to be taken twice daily until Week 52, whereas the prednisolone regimen was tapered off by Week 20. Both treatments were given in combination with SoC, which comprised of an investigator's choice of background induction therapy; rituximab or cyclophosphamide. Maintenance oral azathioprine was provided to all patients who received a cyclophosphamide-based induction regimen. Patients who received a rituximab-based regimen did not receive maintenance therapy after induction therapy. The protocol permitted supply of "non-study supplied glucocorticoids" in both arms, however the study protocol indicated that these were to be avoided as much as possible.

The co-primary efficacy endpoints were remission at Week 26 and sustained remission at Week 52. Remission was defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26. Secondary endpoints included; early remission (by Week 4), Glucocorticoid Toxicity Index (GTI) during the first 26 weeks of treatment, change from

baseline renal disease, and EQ-5D-5L Visual Analogue Score (VAS). After the 52-week treatment period, the majority of patients entered an eight week follow-up study. Most patients (70%) were newly diagnosed. The median age across both arms was 60.9 years. The most frequent SoC background treatment agent was rituximab, with the remaining patients receiving either IV or oral cyclophosphamide, followed by azathioprine maintenance treatment.

Avacopan was found to be non-inferior to the prednisolone-arm at week 26, with 72.3% of patients achieving remission compared to 70.1% in the prednisolone arm ($p<0.0001$). Avacopan demonstrated superior efficacy in sustaining remission at the Week 52 endpoint ($p=0.007$), with 65.7% of patients in the avacopan arm achieving remission at Week 52 compared to 54.9% in the prednisolone arm. Secondary endpoints were considered to be supportive of the benefit of avacopan. Over 52 weeks of the trial, glucocorticoid exposure was 56% lower in the avacopan-based regimen group, with a mean cumulative glucocorticoid dose during the treatment period of 1,675.5 mg for the avacopan group versus 3,846.9mg for the prednisone group, driven by study design. Overall, the use of avacopan was associated with statistically less glucocorticoid-induced toxicity relative to prednisone for both scores of the GTI. EQ-5D-5L VAS scores increased markedly during the study in both study arms, however, the differences between avacopan and comparator arms were minor. The short duration of the ADVOCATE study and follow-up period limited the assessment of long-term effects of avacopan treatment, which are of interest given the need for maintenance therapy in the majority of patients, and given the potential need for reinduction in the event of relapse.

The Review Group had several concerns regarding the generalisability of the trial to SOC in Ireland, in particular the composition of the comparator arm upon completion of the tapered prednisolone regimen. In practice, patients are expected to receive maintenance therapy with either rituximab or azathioprine, and low-dose glucocorticoids after induction of remission. While the protocol permitted supply of “non-study supplied glucocorticoids” in both arms, these were to be avoided as much as possible. The generalisability of the maintenance treatment in the comparator arm is also a limitation of the trial, given the use of maintenance rituximab in clinical practice.

2. Safety of avacopan

The safety analysis set of the ADVOCATE trial included 166 and 164 patients in the avacopan and prednisolone arms, respectively. In which, the median duration of exposure was 364 days for avacopan and 140 days for prednisolone. Safety data should be considered in the context that both avacopan and prednisolone were provided alongside background therapy (i.e rituximab/cyclophosphamide/azathioprine) and that a proportion of patients received non-study supplied glucocorticoids. Nearly all patients (98.8% and 98.2%) reported at least one treatment emergent adverse event, however the overall number was lower in the avacopan arm. Discontinuation due to adverse events were similar between patients in the avacopan-based and prednisone-based regimen groups (16.3% vs 17.1%). The most common adverse reactions were nausea (23.5%), headache (20.5%), white blood cell count decreased (18.7%), upper respiratory tract infection (14.5%), diarrhoea (15.1%), vomiting (15.1%), and nasopharyngitis (15.1%). The most common serious adverse reactions were liver function abnormalities (5.4%) and pneumonia (4.8%). Given the hepatotoxic potential of avacopan, the additive effect of these drugs on the liver may further increase the risks compared to when the drugs are given as monotherapy.

Use of avacopan is intended as a strategy to reduce use of glucocorticoids, which have a significant side-effect profile. The proportion of patients experiencing a glucocorticoid-related adverse event was lower in the avacopan arm compared with the prednisolone arm (66.3% vs 80.5%). It is noted that the safety data are limited by the trial duration.

3. Cost effectiveness of avacopan

Methods

A state-transition model, comprising nine health states was submitted by the Applicant. These health states consist of an active disease state (where patients enter the model), three remission states, three relapse states, end stage renal disease (ESRD) and death. The treatment effects captured by the model were an increase in the rate of remission, and reductions in the rate of relapse, death and developing ESRD. The definition of the remission health states, in accordance with the ADVOCATE trial, includes patients achieving a BVAS of

0 and not taking glucocorticoids within four weeks of the end of the six-month induction period. However, clinical opinion obtained by the Review Group indicated that in practice, remission is also considered to have been achieved if patients have a BVAS score of zero, even if they were still taking some glucocorticoids. Transitions between the relapse and remission health states were based on data from the ADVOCATE trial. The key efficacy inputs to the model were remission at week 26, sustained remission at week 52 and week 60. Estimates from the published literature were used to inform transitions into the ESRD health state. Background mortality rates were based on Irish life tables, with adjustments accounting for the increased mortality rates associated with both AAV and ESRD. As avacopan has been shown to reduce glucocorticoid use, and the incidence of serious infections, the Applicant assumed that avacopan would in turn reduce deaths due to serious infections caused by glucocorticoids The assumption that avacopan will reduce deaths is based on the glucocorticoid sparing benefits of avacopan, and not on any empiric evidence of mortality benefit.

The population characteristics in the model were based on the ADVOCATE trial. The model intervention and comparator reflected the ADVOCATE trial, consisting of avacopan with SoC, or a tapered prednisolone regimen with SoC, respectively. SoC comprised of a weighted combination of either rituximab or cyclophosphamide, followed by azathioprine. In which, it was assumed that 64.8% and 35.2% received a rituximab and cyclophosphamide based regimen, respectively, based on the ADVOCATE trial. The Applicant base case assumed that patients in the intervention arm received induction with avacopan once and are treated with rituximab/cyclophosphamide if required for subsequent induction therapy. It is possible that in clinical practice, avacopan may be used to induce remission more than once, however there is currently a lack of evidence supporting the efficacy of recurrent use of avacopan. The Applicant assumed a relative dose intensity of 86.4% for avacopan and 98.4% for prednisolone, based on the ADVOCATE trial.

The incidence of adverse events and HRQoL utilities were directly informed by the ADVOCATE trial in the Applicant base case, with those related to the ESRD health state informed by the literature. The Review Group had several concerns regarding this approach, due to the short duration of the ADVOCATE trial and its limited generalisability to clinical

practice. Data on the frequency and length of hospitalisations in the ADVOCATE trial were combined with unit costs obtained from the HPO 2022 Admitted Patient Price List, to inform resource use costs.

The Review Group identified a number of limitations in the Applicant's model, which were addressed through changes in the NCPE-adjusted base case. These changes included: adjustment of the HRQoL utilities to explicitly model glucocorticoid-related AEs based on data from an analysis commissioned by the Applicant using data from the Clinical Practice Research Datalink (CPRD)– Hospital Episode Statistics linked database; use of a pooled average of two plausible sources of data for ESRD transitions; expansion of the definition of remission to include low-dose glucocorticoid use; use of a more representative HRQoL utility value for dialysis; age adjustment of HRQoL utilities; and assumption of 100% RDI. The base case analysis and scenario analyses were conducted from the perspective of the Health Service Executive (HSE) in Ireland, considering only direct medical costs. The model reports life years, quality adjusted life years (QALY) and costs per treatment cohort as well as the incremental cost-effectiveness ratios (ICERs). The analysis was conducted from the perspective of the HSE.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The probability of cost-effectiveness for avacopan plus SoC versus prednisolone plus SoC (in both the Applicant's base case and the NCPE-adjusted base case analyses) was 0% at a threshold of €20,000/QALY and €45,000/QALY, respectively. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE base case related to relative risk of death across a number of states and times. In a scenario analysis in which the efficacy of avacopan in reducing infection-related mortality is removed, the incremental cost-effectiveness ratio increases to €1.1 million per QALY.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Prednisolone + SoC	€307,986	6.50	-	-	-
Avacopan + SoC	€338,489	6.75	€30,606	0.25	€123,691

ICER: Incremental cost-effectiveness ratio; SoC: Standard of care; QALY: Quality-Adjusted Life Year.

[a] Corresponding probabilistic ICER using 1,000 iterations =€129,281/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and benefits

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Prednisolone + SoC	€299,806	6.56	-	-	-
Avacopan + SoC	€344,084	6.65	€44,278	0.088	€502,953

ICER: Incremental Cost-Effectiveness Results; QALY: Quality Adjusted Life Year; SoC: Standard of Care

[a] Corresponding probabilistic ICER using 1,000 iterations = €496,591/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and benefits.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a 76.3% and 72.8% reduction in the price of avacopan was required to meet the €20,000 per QALY and €45,000 per QALY thresholds respectively.

4. Budget impact of avacopan

The price to wholesaler for avacopan (180 tablets x 10mg) is €6,570.84. The total cost of avacopan, without SoC therapy and assuming a treatment course of 52 weeks, is €80,262. The cost for a tapered prednisolone course, without SoC and assuming a treatment course of 20 weeks, is €44. The Applicant submitted a budget impact model estimating the population of eligible patients with severe, active GPA/MPA and the proportion expected to receive treatment with avacopan if reimbursed in Ireland. The budget impact model has been reviewed by the NCPE Review Group, however many of the inputs are very uncertain and there is therefore considerable uncertainty associated with the budget impact estimates. The Applicant predicted that among the incident and prevalent eligible population, 6 patients will be treated in Year 1 rising to 27 patients in Year 5, resulting in a total of 93 patients receiving treatment over five years. The Applicant estimated a 5-year cumulative gross drug budget impact for avacopan (not including SoC therapy) of €4.1 million (VAT not applicable). The Review Group considers the Applicant's budget impact to be considerably underestimated due to the omission of avacopan costs for some prevalent patients in the model, and that the annual drug budget impact could be as high as €6.8 million. Clinical opinion obtained by the NCPE Review Group anticipates high levels of uptake in the eligible

patient population given the demand for alternatives to glucocorticoids. Therefore, NCPE Review Group considered that these estimates are likely to be underestimated.

5. Patient Organisation Submission

A patient organisation submission was received from Vasculitis Ireland Awareness.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that avacopan not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.