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National Health Care Institute
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Medicinal Products

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2023009226

Our reference
2023009226

Date 15 June 2023
Re: GVS advice on avacopan (Tavneos®)

Dear Mr Kuipers,

In a letter dated 5 January 2022 (reference CIBG-21-03111), the Minister of Medical Care and Sport asked the National Health Care Institute to carry out a substantive assessment of whether the medicinal product avacopan (Tavneos®) is interchangeable with another medicinal product that is included in the Medicine Reimbursement System (GVS).

Avacopan (Tavneos®), 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).

In April 2022, the National Health Care Institute advised you not to include avacopan in the GVS. The cost-effectiveness analysis submitted by the marketing authorisation holder was of insufficient quality, which meant the National Health Care Institute was unable to advise you about any price negotiation.
The MAH has since submitted an updated cost-effectiveness analysis, which has been assessed by the National Health Care Institute.
Avacopan can be placed in List 1B. The medicinal product complies with the established medical science and medical practice for the aforementioned indication and has a therapeutic added value compared to glucocorticoids. On the basis of a conservative cost-effectiveness analysis, the National Health Care Institute considers a discount of at least 80% appropriate.

We would like to explain our findings and final conclusion below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. In this decision, we weigh the matter, both in a scientific sense and from a social basis, and we weigh the aspects of efficiency and transparency. The National Health Care Institute assessed avacopan on the basis of the four package criteria[1]: effectiveness[2], cost-

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl
[2] Assessment of the established medical science and medical practice 2023. National Health Care Institute, Diemen. Via: www.zorginstituutnederland.nl

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effectiveness[3], necessity and feasibility. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on determining the budget impact and cost-effectiveness; and the Insured Package Advisory Committee for the social assessment. We also consulted stakeholders during the assessment process.

Assessment of interchangeability
To determine the place of a medicinal product in the GVS, its interchangeability with medicinal products already included in the GVS must first be assessed. No other medicinal product has been included in the GVS that is specifically registered for the indication 'severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)'. The Dutch guideline shows that the following medicinal products can be used for GPA and MPA: prednisone, methylprednisolone, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, and rituximab.

Rituximab and cyclophosphamide are inpatient medicines and are not included in the GVS. As a result, these medicinal products are not eligible for an review of interchangeability with avacopan. Nor are the other medicinal products mentioned above eligible for any further review of interchangeability, as they do not have a similar therapeutic area.

Based on the above, avacopan (Tavneos®) cannot be placed in List 1A. A review should be carried out to determine whether avacopan is eligible for inclusion in List 1B.

Therapeutic value
The National Health Care Institute has concluded that avacopan (Tavneos®), in combination with a rituximab regimen or cyclophosphamide regimen, complies with established medical science and medical practice for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). In relapse prevention, avacopan has a clinically relevant effect that is superior to the prednisone tapering schedule. Currently, these patients are treated long term with very high doses of glucocorticoids, which can cause many unpleasant side effects. Treatment with avacopan reduces the need for glucocorticoids in these patients. The occupational group sees this as the main benefit of avacopan. The reduced use of glucocorticoids in the study (with a follow-up duration of 52 weeks) resulted in reduced toxicity (which is considered crucial). No clinically relevant improvement was reported for the incidence of serious undesirable effects and the number of patients who discontinue treatment. The quality of life of these patients improved statistically significantly, but it is uncertain whether this effect is also clinically relevant. Treatment with avacopan reduces the risk of relapse and reduces the need for patients to take glucocorticoids, which cause many unpleasant side effects. It can therefore be concluded that avacopan has an added value compared to glucocorticoids.

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

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Budget impact analysis
Avacopan costs €60,549 per one-year induction treatment (with 86.4% patient compliance). It is assumed that 1,254 to 1,391 patients per year will be eligible for avacopan. Based on a market penetration of 15% in year 1, rising to 45% in year 3,626 patients will eventually start an induction treatment with avacopan in year 3. In addition, a small subgroup has been identified that is assumed to have a chronic need for avacopan. This involves 40 patients in year 3, assuming a market penetration of 100%. The total budget impact (without price negotiations) in year 3 is expected to be €33.1 million.

Cost-effectiveness analysis
The National Health Care Institute concludes that the ICER reported by the marketing authorisation holder is probably too favourable. The pharmaco-economic model provided is of sufficient methodological quality to calculate an alternative ICER (range). This will allow the results to be used in the decision-making process. The marketing authorisation holder reports an ICER of €365,614 per gained QALY for avacopan compared to prednisone. The National Health Care Institute has opted to use an ICER range of €365,614 - €555,856 per QALY gained. This range has been derived from an assumption about the results on renal function (eGFR). The National Health Care Institute takes the view that the marketing authorisation holder has made a too favourable assumption (for them), while the data from the clinical trial shows something else. Furthermore, there are two main uncertainties, namely the modelled effect on mortality and the choices about modelling the side effects.

The National Health Care Institute has used a reference value of €20,000 per QALY gained.. Based on the lower limit of the ICER range, the price reduction should be 75% to get the ICER under the reference value of €20,000. Based on the upper limit of the ICER range, the price reduction should be 80%.

It is good to note here that the QALY gain for avacopan is between 0.07-0.11. This means that this medicinal product results in a very small added benefit relative to the current standard treatment. However, the effect achieved on preventing relapse and reducing glucocorticoid use and toxicity is statistically significant and clinically relevant. The National Health Care Institute therefore concludes that there is an added value compared to standard treatment. The small QALY gain translates into the high price reduction needed to arrive at a cost-effective price. In addition, the reported ICER range is large, while the corresponding recommended price reductions show a range of merely 5%. This can be explained by the fact that the costs of the medicinal products are only a relatively small part of the total costs and by the fact that ICER does not change linearly because this is a ratio. The achieved QALY gains and the current list price of avacopan are disproportionately far apart. The National Health Care Institute arrives at a much lower price based on the relatively low QALY gains. To charge a higher price, far more health benefits are needed.

Orphan drugs arrangement
An orphan drugs arrangement will be set up, in collaboration with the occupational group, to monitor and track the appropriate use of avacopan. This establishes agreements on appropriate use, including indications, stop criteria, the role of expertise centres in the care process, and monitoring. The National Health Care Institute will also involve the patients' association and health care insurers in

these agreements.

Final conclusion
The National Health Care Institute recommends that you include avacopan in combination with a rituximab or cyclophosphamide regimen for the treatment of adult patients with severe active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) in the insured package, provided that a price reduction is achieved and an orphan drugs arrangement is established.
In view of the uncertainties, the Insured Package Advisory Committee (ACP) takes the view that a higher price reduction than the calculated 75% to 80% is necessary. On the basis of a conservative cost-effectiveness analysis, the National Health Care Institute considers a discount of at least 80% appropriate. If a price reduction of 80% is achieved, this will mean a budget impact of €6.6 million in the third year.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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