Annex

Scientific conclusions

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Tavneos (avacopan) is a centrally authorised medicinal product, which was granted a marketing authorisation in the European Union (EU) on 11 January 2022 based on an application in accordance with Article 8(3) of Directive 2001/83/EC. 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).

The marketing authorisation application (MAA) for Tavneos submitted by the applicant, Vifor Fresenius Medical Care Renal Pharma France, included one phase 3 clinical study (ADVOCATE, also known as Study CL010_168) and two supportive phase 2 clinical studies (CL002_168 and CL003_168). The ADVOCATE study (sponsor: ChemoCentryx) was considered the pivotal study for the assessment of the clinical efficacy of Tavneos in its therapeutic indication.

In January 2026, EMA became aware of new information which raised questions regarding the data integrity of the ADVOCATE study. The new information specifically pertained to the sponsor's handling of the ADVOCATE study database. This raised serious questions as to whether amendments to the study data had taken place, whether such actions (if any) were consistent with the pre-specified protocol and statistical analysis plan for the study, and whether this new information could potentially impact the reliability of the ADVOCATE study and the assessment of the results, previously conducted based on the information available to EMA at the time of the granting of a marketing authorisation for Tavneos by the EC.

On 29 January 2026, the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the Committee for Medicinal Products for Human Use (CHMP) to assess the impact of the above concerns on the benefit-risk balance of Tavneos, and to give its opinion on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The review of the data provided in the context of the Article 20 referral procedure has revealed serious breaches to GCP principles in the handling of primary endpoint data in the pivotal clinical study ADVOCATE.

The sponsor personnel reviewed unblinded efficacy data after an initial database lock (05 November 2019) and detected that superiority at week 52 had not been demonstrated. Thereafter, 9 patients were re-adjudicated based on knowledge of treatment outcomes, after which the primary analysis was rerun resulting in a change from a non-significant to a statistically significant result for superiority at week 52. The sponsor did not disclose the original analysis and post-unblinding data modifications in the initial MAA or post-authorisation procedures. On the contrary, the clinical study report specifically stated that the unblinding process outlined in the protocol has been followed. While the marketing authorisation holder (MAH) has justified the re-adjudication on the grounds of errors in the initial adjudication, review of the patient level data and the adjudication rules and endpoint definitions do not support this statement. Further, the handling of the data, as described, is not compliant with the good clinical practice (GCP) principles (e.g. ICH E6 Good Clinical Practice and ICH E9 Statistical Principles for Clinical Trials). The impact of this breach cannot be isolated to a certain part of the data. Taken together, these issues lead to the conclusion that the study as a whole cannot be considered GCP compliant and reliable.

The ADVOCATE study was the single, pivotal study supporting the initial approval of Tavneos. In this study, according to the clinical study report submitted as part of the MAA, non-inferiority was shown for remission at week 26, while superiority compared to the comparator was documented at week 52 for sustained remission. At the time of the marketing authorisation approval, it was considered that for remission at week 26, the interpretation of non-inferiority was complicated as both arms received

additional immunosuppressive induction treatment. Therefore, an important deciding factor in favour of the positive benefit-risk balance at the time of the granting of the MA for Tavneos was based on superiority in the primary efficacy endpoint at week 52. For the reasons explained above, it is now clear that superiority at week 52 was never demonstrated. The data presented as part of the MAA for this medicinal product, which formed the basis of the original benefit-risk assessment at that time, were therefore incorrect and misleading in this respect.

The MAH has claimed that the data at initial database lock are GCP compliant and that they can be relied upon to demonstrate the positive benefit-risk balance. However, these data cannot be used to support the efficacy, since the study is non-GCP compliant, as described above. Furthermore, even if the results based on the initial database lock of 05 November 2019 were to be considered reliable as claimed by the MAH, the main efficacy result would be non-inferiority of avacopan (administered up to 52 weeks) compared with the comparator (placebo together with an initial 20-week prednisone course), at weeks 26 and 52. Further, the ADVOCATE secondary endpoints, such as the glucocorticoid (GC) toxicity index, were not controlled for multiplicity and are affected by the same limitations of study design and reliability that apply to the primary endpoints.

Additional post-marketing evidence regarding the efficacy of avacopan, including the observational post-marketing safety study AVACOSTAR, is unconvincing, demonstrating limited or no clinically meaningful benefit, and is further constrained by the methodological limitations inherent to observational studies. While some studies may suggest a potential GC-sparing effect of avacopan, these findings are subject to significant limitations in study design and lack the robustness required to support efficacy of Tavneos. Overall, this evidence cannot replace the evidence from an adequately designed and GCP-compliant phase 3 study.

Regarding the safety profile of avacopan, a number of fatal cases of drug induced livery injury and/or vanishing bile duct syndrome have been reported after the initial MA, and the last 3 periodic safety update report single assessment (PSUSA) procedures resulted in updates to the product information accordingly, to minimise the serious risk of liver injury. In particular, in the last PSUSA, emerging safety information related to this risk led to the recommendation to introduce more stringent monitoring advice during the first 3 months of treatment.

On balance, considering that the pivotal study supporting the marketing authorisation is considered as not reliable due to the serious GCP breach, it is concluded that there is no longer demonstration of benefit outweighing the risks of Tavneos, in particular the serious hepatic risks.

CHMP acknowledges that Tavneos is indicated as an adjunctive treatment of a serious rare disease associated with high morbidity and mortality. It is also recognised that the therapeutic options are limited. Nevertheless, avacopan does not replace the established backbone therapy, namely rituximab or cyclophosphamide in combination with GCs. Therefore, in the absence of avacopan, effective treatment options for GPA and MPA remain available. This contextualises the therapeutic role of avacopan as an optimisation strategy rather than an indispensable treatment.

While it is acknowledged that the MAH has indicated the possibility of conducting a new post-authorisation efficacy study aiming to provide data on the efficacy of Tavneos in the future, this has no bearing on the present conclusion, which is based on the data available at present.

Lastly, it is noted that the validity of the marketing authorisation for Tavneos ends in January 2027 and the marketing authorisation will expire if not renewed, which would require demonstration of a positive benefit-risk balance. The MAH has no ongoing or planned alternative clinical study that is adequately designed to replace the ADVOCATE study to demonstrate a positive benefit-risk balance in a defined patient population, before the marketing authorisation is due to expire (as required per the 'Guideline on the processing of renewals in the centralised procedure', EMEA/CHMP/2990/00 Rev.4).

Therefore, CHMP could not identify any condition that could be fulfilled to demonstrate a positive benefit-risk balance for Tavneos.

Overall, the CHMP considers that the benefit-risk balance of Tavneos is negative and that the particulars supporting the marketing authorisation are incorrect. Therefore, the revocation of the marketing authorisation is recommended.

CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Tavneos.
- The CHMP reviewed the totality of the available data provided by the marketing authorisation holder in writing and in an oral explanation, including the new information pertaining to the data handling of the ADVOCATE study, the pivotal study supporting the initial marketing authorisation application for Tavneos. In addition, CHMP considered the views of patient representatives and healthcare professional representatives presented during the oral explanation, as well as written interventions received from third parties.
- The CHMP noted that the data provided at the time of the assessment of the marketing authorisation application for the ADVOCATE study were incorrect and misleading.
- The CHMP concluded that the ADVOCATE study was conducted in breach of good clinical practice principles. As a result of that breach, the results of the study cannot be relied upon to demonstrate efficacy. Further, the additional, available post-marketing authorisation data is not considered sufficient to provide confirmatory evidence which had initially been provided by the single pivotal study (ADVOCATE) to demonstrate the clinical benefit of Tavneos in its authorised indication.
- The CHMP also noted the known safety profile of Tavneos, in particular the serious hepatic risks. These risks are no longer outweighed by an established benefit.
- Furthermore, the CHMP could not identify any feasible condition that could be fulfilled to demonstrate a positive benefit-risk balance for Tavneos.

The Committee, as a consequence, considers that the benefit-risk balance of Tavneos is not favourable, and that the particulars supporting the marketing authorisation as provided for in Article 8 of Directive 2001/83/EC are incorrect.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisation for Tavneos.