Summary of risk management plan for Tavneos (avacopan)

This is a summary of the Risk Management Plan (RMP) for Tavneos. The RMP details important risks of Tavneos, how these risks can be minimised, and how more information will be obtained about Tavneos' risks and uncertainties (missing information).

Tavneos's Summary of Product characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Tavneos should be used.

This summary of the RMP for Tavneos should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Tavneos's RMP.

I The Medicine and What it is Used for

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) (see SmPC for the full indication). It contains avacopan as the active substance and it is given as 10 mg hard capsules for oral administration.

Further information about the evaluation of Tavneos's benefits can be found in Tavneos's European Public Assessment Report, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/tavneos).

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Tavneos, together with measures to minimise such risks and the proposed studies for learning more information about Tavneos's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that can affect the safe use of Tavneos is not yet available, it is listed under missing information below.

II.A List of Important Risks and Missing Information

Important risks of Tavneos are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tavneos. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Liver injury
Important potential risk	Cardiovascular safety Serious infection Malignancy
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Liver injury	
Evidence for linking the risk to the medicine	In a small number of cases, hepatic transaminases and bilirubin elevations have been observed in Phase 2 and in Phase 3 studies. These occurred in a background of co-administered drugs, such as trimethoprim/sulfamethoxazole which are known liver toxins, so clear and direct causality with avacopan could not be established. These elevations reversed with withdrawal of study drug (and trimethoprim/sulfamethoxazole). Monitoring for liver enzymes is readily achieved in clinical practice because the ANCA-associated vasculitis specialists are already implementing such monitoring for the other drugs that are co-administered (cyclophosphamide and rituximab).
Risk factors and risk groups	Patients with severe hepatic impairment, patients concomitantly treated with CYP3A4 inhibitors.

Important Identified Risk: Liver injury	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4, and Section 4.8; PIL Section 2 and 4 • Recommendation for liver function test monitoring, awareness for patients with liver disorders is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None
Important Potential Risk: Cardiovascular safety	
Evidence for linking the risk to the medicine	Cardiovascular safety is high in patients with AAV. Due to the small number of patients who demonstrated cardiac abnormalities in patients treated with avacopan, careful monitoring is required
Risk factors and risk groups	AAV patients have a higher risk for cardiovascular disorders
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PIL Section 2 • Information regarding cardiac disorder awareness for patients is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None
Important Potential Risk: Serious infection	
Evidence for linking the risk to the medicine	The risk of infections in AAV is considered high; however, this has yet to be robustly quantified. Studies of infection in AAV report variable risks ranging from 6 to 67% [68]. Based on the available data from Phase 3, the incidence of serious infections was 15.2% in the prednisone group versus 13.3% in the avacopan group. Considering the seriousness of AAV and the severity of infections, close monitoring is required to further evaluate the safety profile for serious infection in patients with AAV treated with avacopan
Risk factors and risk groups	Active disease remains one of the main causes of death in patients with AAV, especially in the first months of follow-up. It is important to identify predisposing factors such as intensive immunosuppressant treatment, severe renal dysfunction and leukopenia, and stratify treatment according to the disease severity
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4 and Section 4.8; PIL Section 2 and 4 • Information regarding seriousness infection is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None
Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	The risk of malignancy is a concern based on the response of the complement system as well as avacopan mechanism of action. Additionally, due to eculizumab similar target as avacopan, malignancies are included within the risk profile for eculizimab as an adverse reaction. Furthermore, avacopan preclinical data is limited, and the phase II and phase III clinical studies mainly excluded subjects with a history or presence of any form of cancer within the 5 years prior to screening. The studies conducted to date were limited with regards to follow-up time and total exposure to provide any substantial assessment to the risk.
Risk factors and risk groups	Active disease in patients with AAV treated in combination with CYC. It is important to identify predisposing factors such as intensive immunosuppressant treatment, and stratify treatment according to the disease severity.

Important Potential Risk: Malignancy	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PIL Section 2 • Information regarding malignancy is included in SmPC Section 4.4 and PIL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

Missing Information: None	
Risk minimisation measures	Routine risk minimisation measures: NA Additional risk minimisation measures: NA

Notes: NA=Not applicable.

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or Specific Obligations of Tavneos.

II.C.2 Other Studies in Post-authorisation Development Plan

Study Category	Study Short Name	Study Full Name	Purpose
3	PASS study	Avacopan Real World Evidence in ANCA-Associated Vasculitis	Evaluate the long-term (beyond 1 year up to 36 months) safety of avacopan in ANCA Vasculitis patients; Estimate the incidence rates of medical events of special interest (e.g., liver injury, serious infections, malignancies and cardiovascular events.

Notes: ANCA=Anti-neutrophil cytoplasmic autoantibody; PASS=Post=Authorisation Safety Study.