SUMMARY OF THE RISK MANAGEMENT PLAN FOR TAVNEOS® (AVACOPAN)

Invented Name:	Tavneos
Active Substance:	Avacopan
Current RMP	EU RMP Version 2.1 dated 4 December 2024 (data lock point 5 January 2024)
Date of the Report:	26 March 2025
Marketing Authorisation Holder:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 9014 St. Gallen Switzerland

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Tavneos is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/ Information sur le Médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Tavneos in Switzerland is the "Arzneimittelinformation/Information sur le Médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Vifor Fresenius Medical Care Renal Pharma Ltd. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tavneos.

TABLE OF CONTENTS

Page

SUMMARY OF THE RMP 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's 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.

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

According to Swiss Label

Tavneos, as an adjunctive treatment to standard immunosuppressive treatment that includes rituximab or cyclophosphamide with glucocorticoids, is indicated for the treatment of adult patients with severe, active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

According to EU SmPC

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).

Tavneos 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).
Risk factors and risk groups	Common risk factors for hepatotoxicity include • Older age • Female gender • Underlying liver diseases (e.g., hepatitis) • Other comorbidities such as acquired immunodeficiency syndrome • Genetic predisposition involving CYP450, HLA alleles and other drug-processing enzymes • Chronic alcohol consumption • Concomitant use of hepatotoxic medications
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4, and Section 4.8; PL Section 2 and 4 • Recommendation for liver function test monitoring, awareness for patients with liver disorders is included in SmPC Section 4.4 and PL 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. A treatment regimen based on the combination with cyclophosphamide followed by azathioprine may carry an increased risk for cardiac disorders as compared to a regimen based on the combination with rituximab.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PL Section 2 • Information regarding cardiac disorder awareness for patients is included in SmPC Section 4.4 and PL 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%. 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; PL Section 2 and 4 • Information regarding seriousness infection is included in SmPC Section 4.4 and PL 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 role of the complement system in tumour biology. Additionally, due to eculizumab affecting similar target as avacopan, malignancies are included within the risk profile for eculizimab as an adverse reaction. Furthermore, nonclinical data from mutagenicity and carcinogenicity studies indicate that avacopan was not mutagenic, clastogenic and carcinogenic in pharmacologically relevant animal species (hamster). The phase 2 and phase 3 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.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PL Section 2 • Information regarding malignancy is included in SmPC Section 4.4 and PL Section 2 • Legal status: Prescription only medication Additional risk minimisation measures: None

Notes: AAV=ANCA-associated vasculitis; ANCA=Anti-neutrophil cytoplasmic autoantibody; CYC=Cyclophosphamide; PL=Package 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	EU PASS AvacoStar	AvacoStar: A Post-Authorisation Safety Study (PASS) to Evaluate the Incidence of Safety Events of Interest in Patients Treated with Avacopan for ANCA-associated Vasculitis (AAV)	Evaluate the long-term (beyond 1 year for at least 4 years up to (LPLV) safety of avacopan in a real-world cohort 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; LPLV=Last patient last visit; PASS=Post=Authorisation Safety Study.