▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

WARNING
Vanishing bile duct syndrome (VBDS), including cases with fatal outcomes, has been reported as a consequence of liver injury in patients using Tavneos. To mitigate the risk of liver injury, liver function must be monitored before and regularly during therapy. Treatment must be re-assessed and stopped based on symptoms severity (See Section 4.4 Special warnings and precautions for use: Hepatotoxicity and Section 4.2 Dosage and Method of administration).

AUSTRALIAN PRODUCT INFORMATION – TAVNEOS® (AVACOPAN) CAPSULES

1 NAME OF THE MEDICINE

Avacopan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10 mg of avacopan.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Hard capsule.

Capsules with yellow body and light orange cap with “CCX168” in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tavneos, in combination with a rituximab or cyclophosphamide based regimen, is indicated for the treatment of adults with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA or MPA.

Dosage

Before initiating Tavneos, perform the following evaluations:
- Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (see Section 4.4 Special warnings and precautions for use).

The recommended dose of Tavneos is 30 mg (3 hard capsules of 10 mg each) taken orally twice daily, morning and evening, with food.

Tavneos should be administered in combination with rituximab or cyclophosphamide. Suitable dosing regimens for these combinations include:

- rituximab for 4 weekly intravenous doses or,
- intravenous or oral cyclophosphamide for 13 or 14 weeks, followed by oral azathioprine or mycophenolate mofetil and,
- glucocorticoids as clinically indicated.

For details on doses, concomitant glucocorticoids and data on efficacy and safety for the combinations, please see Sections 4.8 Adverse effects (Undesirable effects) and 5.1 Pharmacodynamic properties.

Clinical study data are limited to 52 weeks of exposure followed by 8 weeks of observation.

Missed doses

If a patient misses a dose, the missed dose is to be taken as soon as possible, unless within three hours of the next scheduled dose. If within three hours, then the missed dose is not to be taken.

Dose management

Treatment must be re-assessed clinically and temporarily stopped if:

- ALT or AST is more than 3 × the upper limit of normal (ULN).

Treatment must be temporarily stopped if:

- ALT or AST > 5 × ULN,
- a patient develops leukopenia (white blood cell count < 2×10^9/L) or neutropenia (neutrophils < 1×10^9/L), or lymphopenia (lymphocytes < 0.2×10^9/L).
- a patient has an active, serious infection (i.e. requiring hospitalisation or prolonged hospitalisation).

Treatment may be resumed:

- upon normalisation of values and based on an individual benefit/risk assessment.

If treatment is resumed, hepatic transaminases and total bilirubin are to be monitored closely.

Permanent discontinuation of treatment must be considered if:

- ALT or AST > 8 × ULN, or
- ALT or AST > 5 × ULN for more than 2 weeks, or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalised ratio (INR) > 1.5, or
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%), or
- an association between avacopan and hepatic dysfunction has been established, or
- ALP ≥ 2 × ULN, or
- presence of clinical symptoms such as jaundice or pruritus.

Immediately and permanently discontinue Tavneos treatment if vanishing bile duct syndrome (VBDS) is suspected (see Section 4.4 Special warnings and precautions for use, subsection Hepatotoxicity).

Method of administration

Tavneos is for oral use.

The hard capsules are to be taken with food and swallowed whole with water and must not be crushed, chewed, or opened.

Grapefruit and grapefruit juice are to be avoided in patients treated with Tavneos (see Section 4.5 Interactions with other medicines and other forms of interactions).

Special populations

Renal impairment

No dose adjustment is needed based on renal function (see Section 5.2 Pharmacokinetic properties).

Tavneos has not been studied in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with an estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m^2, who are on dialysis, in need of dialysis or plasma exchange.

Severe disease manifested as alveolar haemorrhage

Tavneos has not been studied in patients with severe disease manifested as alveolar haemorrhage.

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

Tavneos has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see Section 4.4 Special warnings and precautions for use).

Elderly

No dose adjustment is required in elderly patients (see Section 5.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of Tavneos in adolescents (12 to 17 years of age) have not yet been established. Currently available data are described in Sections 4.8 Adverse Effects (Undesirable Effects) and 5.1 Pharmacodynamic properties but no recommendation on dosage can be made.

The safety and efficacy of Tavneos in children below 12 years of age have not yet been established.

Tavneos is not recommended for use in adolescents and children below 17 years of age.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatotoxicity

Serious adverse reactions of elevated hepatic transaminases with elevated total bilirubin have been observed in patients receiving Tavneos in combination with cyclophosphamide (followed by azathioprine or mycophenolate) or rituximab and trimethoprim and sulfamethoxazole (see Section 4.8 Adverse effects (Undesirable effects)).

Vanishing bile duct syndrome (VBDS), including cases with fatal outcomes, has been reported as a consequence of liver injury in the post marketing setting. Most reported cases occurred in Japan in patients aged 65 years and older, but VBDS may occur in patients of any age or ethnicity who are receiving Tavneos (see Section 4.8 Adverse effects (Undesirable effects)).

Tavneos must be avoided in patients with signs of liver disease, such as elevated AST, ALT, ALP, or total bilirubin > 3 × ULN.

Liver function test including hepatic transaminases and total bilirubin must be obtained prior to initiation of therapy (see Section 4.2 Dose and method of administration).

Liver function must be monitored at least every 2 weeks after the start of therapy for the first 3 months, followed by every 4 weeks for the next 3 months of treatment, and as clinically indicated thereafter (see Section 4.2 Dose and method of administration).

Blood and immune system

White blood cell (WBC) count must be obtained prior to initiation of therapy and patients must be monitored as clinically indicated and as part of the routine follow-up of patient's underlying condition (see Section 4.2 Dose and method of administration).

Treatment with avacopan must not be initiated if WBC count is $< 3.5 \times 10^9$/L, or neutrophil count is $< 1.5 \times 10^9$/L, or lymphocyte count is $< 0.5 \times 10^9$/L.

Patients receiving avacopan must be instructed to report immediately any evidence of infection, unexpected bruising, bleeding, or any other manifestations of bone marrow failure.

Serious infections

Serious infections have been reported in patients receiving combination agents for treatment of GPA or MPA, including Tavneos in combination with rituximab or cyclophosphamide (see Section 4.8 Adverse effects (Undesirable effects)).

Patients must be assessed for any serious infections.

Avacopan has not been studied in patients with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infections. Before and during treatment, patients must notify their physician if they have been diagnosed with tuberculosis, hepatitis B, hepatitis C, or HIV infection. Be cautious when treating patients with a history of tuberculosis, hepatitis B, hepatitis C, or HIV infection.

Avacopan does not decrease the formation of the membrane attack complex (C5b-9) or terminal complement complex (TCC). No cases of *Neisseria meningitidis* have been identified in the avacopan clinical programme. Monitor patients treated for ANCA-associated vasculitis according to standard practice for clinical signs and symptoms of *Neisseria* infections.

Pneumocystis jirovecii pneumonia prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis is recommended for adult patients with GPA or MPA during Tavneos treatment, as appropriate according to local clinical practice guidelines.

Immunisation

The safety of immunisation with live vaccines, following Tavneos therapy has not been studied. Administer vaccinations preferably prior to initiation of treatment with Tavneos or during quiescent phase of the disease.

Angioedema

Angioedema has been reported in patients receiving Tavneos (see Section 4.8 Adverse effects (Undesirable effects)).

Patients must notify their physician if they develop any symptoms such as swelling of the face, lips, or tongue, throat tightness, or difficulty breathing.

Tavneos must be withheld in cases of angioedema.

Interaction with strong CYP3A4 inducers

The use of strong CYP3A4 enzyme inducers (e.g., carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with Tavneos is to be avoided (see Section 4.5 Interactions with other medicines and other forms of interactions).

Patients anticipated to require long-term administration of these medicinal products are not to be treated with Tavneos.

If short-term co-administration cannot be avoided in a patient already using Tavneos, the patient must be closely monitored in case of any reoccurrence of disease activity.

Interaction with strong CYP3A4 inhibitors

Strong CYP3A4 enzyme inhibitors (e.g., boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) should be used with caution in patients who are being treated with avacopan (see Section 4.5 Interactions with other medicines and other forms of interactions).

Grapefruit and grapefruit juice can increase the concentration of avacopan; therefore, grapefruit and grapefruit juice are to be avoided in patients treated with avacopan.

PEG-40 hydrogenated castor oil content

This medicinal product contains PEG-40 hydrogenated castor oil, which may cause stomach upset and diarrhoea.

Cardiac disorders

Patients with GPA or MPA are at risk of cardiac disorders such as myocardial infarction, cardiac failure, and cardiac vasculitis.

Serious adverse events (SAEs) of cardiac disorder have been reported in patients treated with avacopan. 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.

Malignancy

Immunomodulatory medicinal products may increase the risk for malignancies. The clinical data are currently limited (see section 5.1 Pharmacodynamic properties).

Use in hepatic impairment

The pharmacokinetic properties of avacopan have been examined in 16 patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. When compared to normal controls, no pharmacologically relevant differences in exposure (mean ratios of C_{max} and area under the curve (AUC) of ≤ 1.3) of avacopan or its major metabolite M1 was observed; therefore, no dose adjustment is necessary (see Section 4.2 Dose and method of administration).

Tavneos has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see Section 4.2 Dose and method of administration).

Use in renal impairment

Based on population pharmacokinetic analysis, the plasma exposure of avacopan is similar between patients with renal impairment and healthy patients. Therefore, no dose adjustment is necessary based on renal function (see Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties).

Tavneos has not been studied in patients with ANCA-associated vasculitis with an eGFR below 15 mL/min/1.73 m², who are on dialysis, in need of dialysis or plasma exchange.

Use in the elderly

Population pharmacokinetic analysis found no significant effect of age (among adults) on the plasma exposure of avacopan; however, there were limited pharmacokinetic data in patients over 75 years of age in clinical studies. No dose adjustment is necessary for elderly patients (see Section 4.2 Dose and method of administration).

The safety profile was similar between patients ≥ 65 years of age and adult patients < 65 years of age in the clinical studies (See Section 4.8 Adverse effects (Undesirable effects)).

Paediatric use

A total of 3 adolescents were studied in the phase 3 study, one in the prednisone group and two in the Tavneos group. There are no data in children below 12 years of age (see Section 5.1 Pharmacodynamic properties). Tavneos is not recommended for use in adolescents and children below 17 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Avacopan is a substrate of CYP3A4. Co-administration of inducers or inhibitors of CYP3A4 may affect the pharmacokinetics of avacopan.

Effect of strong CYP3A4 inducers on avacopan

Co-administration of avacopan with rifampicin, a strong CYP3A4 enzyme inducer, resulted in a decrease in area-under-the-concentration time curve (AUC) and maximum plasma concentration (C_{max}) of avacopan by approximately 93% and 79%, respectively. Since this interaction may result in loss of efficacy of avacopan, the use of strong CYP3A4 enzyme inducers (e.g., carbamazepine, enzalutamide, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with avacopan is to be avoided (see Section 4.4 Special warnings and precautions for use).

Patients anticipated to require long-term administration of these medicinal products are not to be treated with avacopan. If short-term co-administration cannot be avoided in a patient already using avacopan, the patient must be closely monitored for any reoccurrence of disease activity.

Effect of moderate CYP3A4 inducers on avacopan

Exercise caution when using moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, and modafinil) prescribed as concomitant medicinal products with Tavneos and carefully evaluate the benefit/risk of avacopan.

Effect of strong CYP3A4 inhibitors on avacopan

Co-administration of avacopan with itraconazole, a strong CYP3A4 enzyme inhibitor, resulted in an increase in AUC and C_{max} of avacopan by approximately 2.2-fold and, 1.9-fold, respectively. Therefore, strong CYP3A4 enzyme inhibitors (e.g., boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) should be used with caution in patients who are being treated with avacopan. Patients must be monitored for potential increase of side effects due to the increased exposure of avacopan.

Grapefruit and grapefruit juice can increase the concentration of avacopan; therefore, grapefruit and grapefruit juice are to be avoided in patients treated with avacopan.

Effect of avacopan on CYP3A4 substrates

Avacopan is a moderate inhibitor of CYP3A4 in vivo and may increase the plasma exposures of concomitant medicinal products that are CYP3A4 substrates with a narrow therapeutic index (e.g., alfentanil, ciclosporin, ergotamine, fentanyl, sirolimus and tacrolimus). Co-

administration of avacopan and simvastatin increases the systemic exposure of simvastatin (see Section 5.2 Pharmacokinetic properties). Be cautious when these medicinal products are used with avacopan. Patients must be managed according to the Product Information documents of the respective medicinal products with a narrow therapeutic index.

Effect of PEG-40 hydrogenated castor oil on sensitive P-glycoprotein (P-gp) substrates

A clinically relevant effect of the excipient PEG-40 hydrogenated castor oil on sensitive P-gp substrates with relatively low bioavailability (e.g., dabigatran etexilate) cannot be excluded. Exercise caution when using low-bioavailability P-gp substrates in patients who are being treated with avacopan.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of avacopan on human fertility.

Avacopan produced no effects on male or female reproductive performance (fertility) in hamsters up to oral doses of 1,000 mg/kg/day administered as 500 mg/kg BID, equivalent to up to 5.8-fold the clinical AUC based on the combined exposures of avacopan and active metabolite M1.

Use in pregnancy – Pregnancy Category D

There are no data from the use of Tavneos in pregnant women.

In an embryofetal development study with pregnant hamsters, oral administration of avacopan during the period of organogenesis from gestation day (GD) 6 to 12, produced an increased incidence of skeletal variations (supernumerary rib) at a maternal oral dose of 1,000 mg/kg/day administered as 500 mg/kg BID, equivalent to 4.0-fold the clinical AUC based on the combined exposures of avacopan and active metabolite M1.

In an embryofetal development study with pregnant rabbits, oral administration of avacopan (GD 6 to 18) caused an increase in the number of abortions at exposures 0.52 times the maximum recommended human dose (MRHD) (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however no evidence of fetal toxicity at oral doses of 200 mg/kg/day, equivalent to 0.52-fold the clinical AUC. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.50 times and higher than the MRHD (on an AUC basis with maternal oral doses of > 30 mg/kg/day).

In a prenatal and postnatal development study with pregnant hamsters, oral administration of avacopan (GD 6 to 20) did not result in adverse effects on growth and development of offspring at maternal oral doses of up to 1,000 mg/kg/day administered as 500 mg/kg BID, equivalent to 3.6-fold the clinical AUC.

Tavneos is not recommended during pregnancy and in women of childbearing potential not using contraception.

Use in lactation

Avacopan has not been measured in milk of lactating animals; however, analysis of avacopan plasma levels in the lactating dams and the plasma levels in nursing offspring showed the presence of avacopan (at a pup to maternal level plasma ration of 0.37), suggesting that avacopan is likely secreted into the milk of lactating hamsters.

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with Tavneos, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Avacopan has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects

An overview of AEs reported in the pivotal phase 3 ADVOCATE study (Study CL010_168) is presented in Table 1. A total of 1,779 treatment emergent adverse events (TEAEs) were reported by 164 patients (98.8%) in the Tavneos group. A total of 2139 TEAEs (20.2% higher than in the Tavneos group) were reported by 161 patients (98.2%) in the prednisone group.

Table 1: Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients in Either Group by SOC/ Preferred Term in Study CL010_168 (Safety Population)

SOC/Preferred Term	Tavneos (N=166)	Prednisone (N=164)
	%	%
Any TEAE	98.8	98.2
Infections and Infestations		
Nasopharyngitis	15.1	18.3
Upper respiratory tract infection	14.5	14.6
Urinary tract infection	7.2	14.0
Sinusitis	6.0	7.3
Oropharyngeal pain	3.6	7.3
Pneumonia	6.6	6.7
Bronchitis	3.0	6.1
Gastrointestinal Disorders		
Nausea	23.5	20.7
Diarrhoea	15.1	14.6
Vomiting	15.1	12.8
Constipation	6.6	6.7
Abdominal pain upper	6.6	6.1
Dyspepsia	3.0	6.1
Musculoskeletal and Connective Tissue Disorders		

SOC/Preferred Term	Tavneos (N=166)	Prednisone (N=164)
	%	%
Muscle spasms	10.8	22.6
Arthralgia	18.7	22.0
Back pain	9.6	13.4
Myalgia	9.6	13.4
Pain in extremity	7.8	7.9
Tremor	1.2	6.1
Paraesthesia	5.4	4.3
General Disorders and Administration Site Conditions		
Oedema peripheral	21.1	24.4
Pyrexia	9.0	11.6
Fatigue	10.2	9.1
Skin And Subcutaneous Tissue Disorders		
Rash	11.4	7.9
Alopecia	4.2	7.3
Pruritus	6.0	6.1
Nervous System Disorders		
Headache	20.5	14.0
Dizziness	6.6	6.1
Investigations		
Weight increased	0.6	10.4
Blood creatinine increased	6.0	4.9
Respiratory, Thoracic and Mediastinal Disorders		
Cough	15.7	15.9
Epistaxis	8.4	12.8
Dyspnoea	4.8	6.7
Metabolism and Nutrition Disorders		
Hypercholesterolaemia	7.2	12.2
Vascular Disorders		
Hypertension	18.1	17.7
Blood and Lymphatic System Disorders		
Anaemia	7.8	11.0
Lymphopenia	3.6	11.0
Leukopenia	7.2	8.5
Increased tendency to bruise	4.2	6.1
Psychiatric Disorders		
Insomnia	7.8	15.2
Immune System Disorders		
ANCA-positive vasculitis	15.7	20.7
Endocrine Disorders		

SOC/Preferred Term	Tavneos (N=166)	Prednisone (N=164)
	%	%
Cushingoid	1.8	5.5

Summary of the safety profile

The most common adverse reactions are 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 are liver function abnormalities (5.4%) and pneumonia (4.8%).

Tabulated list of adverse reactions

The adverse reactions observed in the ANCA-associated vasculitis pivotal phase 3 study in patients treated with Tavneos are listed in Table 2 by system organ class (SOC) and by frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to 1/10)	Uncommon (≥ 1/1,000 to 1/100)	Not known
Infections and infestations	Upper respiratory, tract infection, Nasopharyngitis	Pneumonia, Lower respiratory tract infection, Influenza, Bronchitis, Cellulitis, Urinary tract infection, Herpes zoster, Sinusitis, Oral candidiasis, Oral herpes, Otitis media, Rhinitis, Gastroenteritis		
Blood and lymphatic system disorders		Neutropenia		
Nervous system disorders	Headache			

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to 1/10)	Uncommon (≥ 1/1,000 to 1/100)	Not known
Gastrointestinal disorders	Vomiting, Diarrhoea, Nausea	Abdominal pain upper		
Hepatobiliary disorders	Liver function test increased*			Vanishing bile duct syndrome
Skin and subcutaneous tissue disorders		Angioedema		
Investigations	White blood cell count decreased**	Blood creatine phosphokinase increased		

* Alanine aminotransferase increased, total blood bilirubin increased, hepatic function abnormal, gamma glutamyl transferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, aspartate amino transferase increased, liver function test increased.
** Includes leukopenia.

Description of selected adverse reactions

Hepatotoxicity

In the pivotal phase 3 study in which 330 patients were dosed, 22 patients (13.3%) in the Tavneos group and 19 patients (11.6%) in the prednisone group had hepatic-related adverse reactions including hepatobiliary adverse reactions and liver enzyme abnormalities.

In the Tavneos group, Liver Function Test (LFT) increased included hepatitis (1.2%), hepatitis cholestatic (0.6%) of which one patient reported both hepatitis and hepatitis cholestatic as a diagnosis, hepatocellular injury (0.6%) in one patient diagnosed with asymptomatic hepatitis, cytolysis and anicteric cholestasis without hepatocellular insufficiency.

Adverse events of hepatobiliary disorders were more frequent in patients treated with a regimen based on a combination with cyclophosphamide followed by azathioprine (10.2%) as compared to those treated with a regimen based on a combination with rituximab (3.7%).

Study medicinal product was paused or discontinued permanently due to LFT increased in 5.4% of patients in the Tavneos group and 3.0% of patients in the prednisone group. Serious adverse reactions of LFT increased were reported in 5.4% of patients in the Tavneos group and 3.7% of patients in the prednisone group. All serious hepatic events resolved with either the withdrawal of avacopan and/or other potentially hepatotoxic medicinal products, including trimethoprim and sulfamethoxazole.

Vanishing bile duct syndrome has been reported in the post-marketing setting (see Section 4.4 Special warnings and precautions for use).

Neutropenia

In the pivotal phase 3 study, neutropenia was reported in 4 patients (2.4%) in each treatment group.

A single case of agranulocytosis was reported each in the prednisone group and in the Tavneos group.

The patient in the Tavneos group was noted to have central neutropenia on a bone marrow biopsy which resolved spontaneously without additional treatment.

Creatine phosphokinase increased

In the pivotal phase 3 study, 6 patients (3.6%) in the Tavneos group and 1 patient (0.6%) in the prednisone group had adverse reactions of increased creatine phosphokinase (CPK).

Hypersensitivity including angioedema

In the pivotal phase 3 study, 2 patients (1.2%) in the Tavneos group had an adverse reaction of angioedema. One patient was hospitalised for the event. Tavneos was paused and both events resolved without sequelae. Tavneos was restarted in one patient and angioedema did not reoccur.

Gastrointestinal disorders

In the pivotal phase 3 study, adverse reactions of gastrointestinal disorders were observed in 74.6% of patients treated with avacopan and a regimen based on a combination with cyclophosphamide followed by azathioprine as compared to those treated with a regimen based on a combination with rituximab (53.3%).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Tavneos was studied in healthy patients at a maximum total daily dose of 200 mg (given as 100 mg twice daily) for 7 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects, and appropriate symptomatic treatment and supportive care are provided.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Complement inhibitors, ATC code: L04AJ05

Mechanism of action

Avacopan is a selective antagonist of the human complement 5a receptor (C5aR1 or CD88) and competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a.

The specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation, migration, and adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and permeability.

Avacopan does not decrease the formation of the membrane attack complex (C5b-9) or terminal complement complex (TCC), which is important in fighting infections with encapsulated bacteria such as *Neisseria meningitidis*.

Pharmacodynamic effects

Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitis disease process.

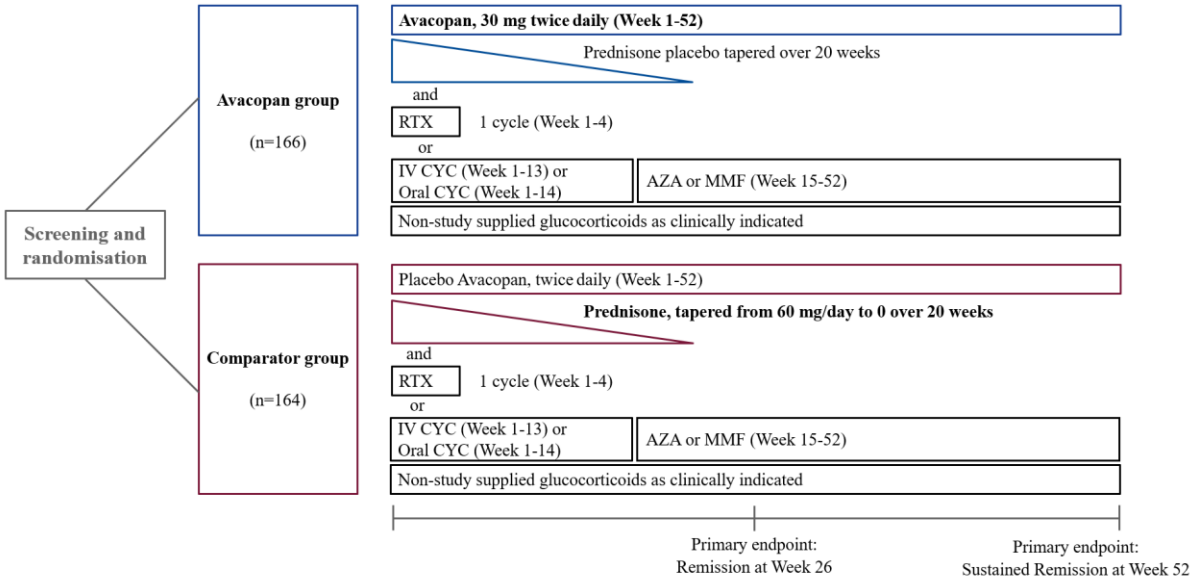
Clinical trials

Clinical efficacy and safety

A total of 330 patients including three females aged 13, 15 and 17 years respectively, with granulomatosis with polyangiitis (GPA) (54.8%) or microscopic polyangiitis (MPA) (45.2%) were treated in the active-comparator, randomised, double-blind, double dummy, multicentre, pivotal phase 3 ADVOCATE study for 52 weeks.

The ADVOCATE study design is depicted in **Figure 1**.

Figure 1: ADVOCATE study design



AZA = azathioprine; CYC = cyclophosphamide; IV = intravenous; MMF = mycophenolate mofetil; RTX =rituximab

Patients were randomised in a 1:1 ratio to one of the two groups:

- Avacopan group (N=166): Patients received 30 mg avacopan twice daily for 52 weeks plus prednisone-matching placebo tapering regimen over 20 weeks,
- Comparator group (N=164): Patients received avacopan-matching placebo twice daily for 52 weeks plus prednisone (tapered from 60 mg/day to 0 over 20 weeks).

All patients in both groups received standard immunosuppressive regimens of either:

- Rituximab at the dose of 375 mg/m² for 4 weekly intravenous doses, or
- Intravenous cyclophosphamide for 13 weeks (15 mg/kg up to 1.2 g every 2 to 3 weeks), and then starting on week 15 oral azathioprine 1 mg/kg daily with titration up to 2 mg/kg daily (Mycophenolate mofetil 2 g daily was allowed in place of azathioprine). If mycophenolate mofetil was not tolerated or not available, enteric coated mycophenolate sodium could be given at a target dose of 1,440 mg/day), or
- Oral cyclophosphamide for 14 weeks (2 mg/kg daily) followed by oral azathioprine or mycophenolate mofetil/sodium starting at week 15 (same dosing regimen as intravenous cyclophosphamide).

For the first rituximab infusion, 100 mg methylprednisolone, or equivalent was given before starting the infusion with rituximab. Glucocorticoid pre-medication for the second, third, and fourth rituximab infusions was allowed.

Dose reductions or adjustments in cyclophosphamide, azathioprine, and mycophenolate were allowed to conform to standard approaches to maximise safety of these medicinal products.

The following study-supplied glucocorticoid tapering schedule was used (Table 3).

Table 3: Glucocorticoid tapering schedule – Prednisone dose (mg per day)

Study Day	Avacopan	Comparator	
	All	≥ 55 kg	< 55 kg
1 to 7	0	60	45
8 to 14	0	45	45
15 to 21	0	30	30
22 to 42	0	25	25
43 to 56	0	20	20
57 to 70	0	15	15
71 to 98	0	10	10
99 to 140	0	5	5
≥141	0	0	0

Non-study supplied glucocorticoids, unless strictly necessary due to a condition requiring the use of glucocorticoids (such as adrenal insufficiency), had to be avoided as much as possible during the study. However, patients who experienced worsening or a relapse of their ANCA-associated vasculitis during the study could be treated with a limited course of glucocorticoids.

Patients were stratified at time of randomisation to obtain balance across treatment groups based on 3 factors:

- Newly-diagnosed or relapsed ANCA-associated vasculitis,
- Proteinase-3 (PR3) positive or myeloperoxidase (MPO) positive ANCA-associated vasculitis,
- Receiving either intravenous rituximab, intravenous cyclophosphamide, or oral cyclophosphamide.

The two treatment groups were well balanced regarding baseline demographics and disease characteristics of patients (Table 4).

Table 4: Selected baseline characteristics in the pivotal phase 3 ADVOCATE study (Intent- to-Treat Population)

Demographic characteristic	Avacopan (N = 166)	Comparator (N = 164)
Age at screening		
Mean (SD), years	61 (14.6)	61 (14.5)
Range, years	13-83	15-88
ANCA-associated vasculitis status, n (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA positivity, n (%)		
PR3	72 (43.4)	70 (42.7)
MPO	94 (56.6)	94 (57.3)
Type of ANCA-associated vasculitis, n (%)		

Demographic characteristic	Avacopan (N = 166)	Comparator (N = 164)
Granulomatosis with polyangiitis (GPA)	91 (54.8)	90 (54.9)
Microscopic polyangiitis (MPA)	75 (45.2)	74 (45.1)
BVAS score		
Mean (SD)	16.3 (5.87)	16.2 (5.69)
eGFR		
Mean (SD), mL/min/1.73 m^2	50.7 (30.96)	52.9 (32.67)
Prior Glucocorticoid Use (during Screening)		
n (%)	125 (75.3)	135 (82.3)
Mean (SD), prednisone-equivalent dose (mg)	907 (1145.9)	978 (1157.5)

ANCA = antineutrophil cytoplasmic autoantibody; BVAS = Birmingham Vasculitis Activity Score; MPO = myeloperoxidase; PR3 = proteinase-3, SD = standard deviation

The aim of the study was to determine if avacopan could provide an effective treatment for patients with ANCA-associated vasculitis, while also allowing for the reduction of glucocorticoids use without compromising safety or efficacy.

The primary objective was to evaluate the efficacy of the above described treatment regimens to induce and sustain remission inpatients with ANCA-associated vasculitis based on the following two primary endpoints:

- the proportion of patients in disease remission 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,
- the proportion of patients in sustained remission defined as remission at week 26 without relapse to week 52, and BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to week 52.

The two primary endpoints were tested sequentially for non-inferiority and superiority using a gatekeeping procedure to preserve the Type I error rate at 0.05.

The prespecified non-inferiority margin for the treatment difference was −20 percentage points.

Results from this study showed that avacopan was non-inferior to prednisone in achieving remission at week 26 and superior to the prednisone group in sustaining remission at week 52

Table 5: Remission at week 26 and sustained remission at week 52 in the pivotal phase 3 ADVOCATE study (Intent-to-Treat Population)

	Avacopan N=166 n (%)	Prednisone N=164 n (%)	Estimate of Treatment Difference in %a	Non-inferiority p-value	Superiority p-value
Remission at Week 26	120 (72.3)	115 (70.1)	3.4	<0.0001	0.2387

	Avacopan N=166 n (%)	Prednisone N=164 n (%)	Estimate of Treatment Difference in %a	Non-inferiority p-value	Superiority p-value
95% CI	64.8, 78.9	62.5, 77.0	−6.0, 12.8		
Sustained Remission at Week 52	109 (65.7)	90 (54.9)	12.5	<0.0001	0.0066
95% CI	57.9, 72.8	46.9, 62.6	2.6, 22.3		

CI = confidence interval
[a] Two-sided 95% CIs are calculated by adjusting for randomisation stratification factors. Non-inferiority and superiority p values are one-sided.

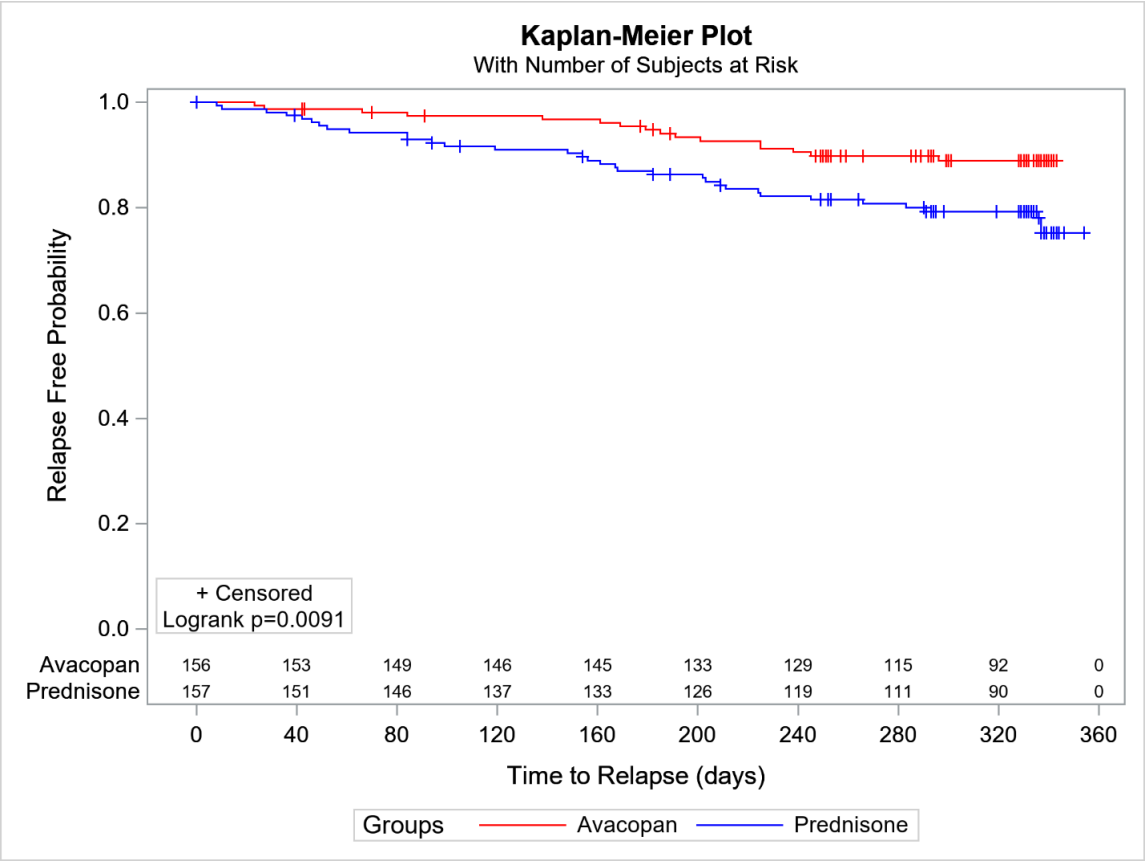
Secondary endpoints

Statistical analyses of secondary and subsequent endpoints showed nominal improvements over treatment with prednisolone. The efficacy observed was consistent across pertinent subgroups, i.e., those with newly-diagnosed and relapsed disease, PR3 and MPO ANCA, GPA and MPA, those receiving cyclophosphamide and those receiving rituximab, and men and women.

Disease relapse

The hazard ratio of the difference in time to relapse was estimated as 0.46, 95% CI (0.25, 0.84). Consequently, the estimated reduction in risk of relapse was 54% in the avacopan compared with the prednisone group. A Kaplan-Meier plot of time to relapse is shown in Figure 2.

Figure 2: Kaplan-Meier Plot of Time to Relapse in Phase 3 Study CL010_168



Estimated glomerular filtration rate (eGFR)

At week 52, the least squares mean (LSM) increase from baseline in estimated glomerular filtration rate (eGFR) was 7.3 mL/min/1.73 m² in the avacopan group (from a baseline of 44.6 mL/min/1.73 m²) and 4.1 mL/min/1.73 m² in the prednisone group (from a baseline of 45.6 mL/min/1.73 m²) (LSM difference 3.2, [95% CI 0.3, 6.1]).

Glucocorticoid toxicity

In the pivotal phase 3 ADVOCATE study, the mean total cumulative prednisone-equivalent dose from day 1 to end-of-treatment was approximately 2.3-fold higher in the comparator group versus the avacopan group (3846.9 mg vs 1675.5 mg, respectively).

The Glucocorticoid Toxicity Index (GTI) assesses glucocorticoid-related morbidity including measures of body mass index, glucose tolerance, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. A higher GTI indicates greater glucocorticoid toxicity. The GTI contains the Cumulative Worsening Score (CWS) that captures cumulative toxicity over the course of time, and the Aggregate Improvement Score (AIS) that captures both improvement and worsening of toxicity over time.

The two GTI scores (CWS and AIS) of the avacopan group versus the comparator group are summarized in **Table 6**. The GTI measures were secondary endpoints in the study and not controlled for multiplicity.

Table 6: Glucocorticoid Toxicity Index results in the pivotal phase 3 ADVOCATE study (Intent-to-Treat Population)

	Avacopan N=166 n (%)	Prednisone N=164 n (%)	Difference between Groups, 95% CI
Cumulative Worsening Score			
Week 13 (least squares mean)	25.7	36.6	−11.0 (−19.7, −2.2)
Week 26 (least squares mean)	39.7	56.6	−16.8 (−25.6, −8.0)
Aggregate Improvement Score			
Week 13 (least squares mean)	9.9	23.2	−13.3 (−22.2, −4.4)
Week 26 (least squares mean)	11.2	23.4	−12.1 (−21.1, −3.2)

* Not adjusted for multiplicity

Incidence of TEAEs considered possibly related to glucocorticoids use based on EULAR-recommended event terms

Consistent with the GTI results, the incidence of pre-identified adverse events considered possibly related to glucocorticoids use based on EULAR-recommended search terms was 80.5% in the prednisone group compared with 66.3% in the avacopan group (difference −14.2%; [95% CI −23.7%, −3.8%]).

Health-related quality of life outcomes

Improvements in physical component score (PCS) of the SF-36 including physical functioning and general health perception at both week 26 and week 52 were observed in the avacopan group compared to the prednisone group. The minimum clinically-important difference (MCID) was reached or exceeded for physical functioning, role physical, and bodily pain domains at week 26 and week 52, and for general health perception at week 52 in the avacopan group.

The mental component score (MCS) of the SF-36 and all other domains showed a numerical improvement in the avacopan group. The MCID was achieved in the avacopan group for MCS at week 52, and for the mental health, role emotional, social functioning, and vitality domains at week 26 and week 52.

EuroQuality of Life-5 domains-5-levels (EQ-5D-5L) visual analogue scale (VAS) was improved from baseline in the avacopan group compared to the prednisone group at week 52. The MCID was achieved in the avacopan group for VAS and index scores at week 52.

Paediatric population

A total of 3 adolescents were studied in the pivotal phase 3 ADVOCATE study, two in the avacopan group and one in the comparator group. One adolescent in the avacopan group discontinued treatment due to worsening renal vasculitis. The second adolescent patient who received avacopan completed treatment, achieved both remission at week 26 and sustained remission at week 52.

The adolescent in the comparator group discontinued treatment due to non-adherence to contraception.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

When administered without food, avacopan peak plasma concentration (C_{max}) occurs at a median time (t_{max}) of approximately 2 hours. Avacopan has shown an approximate dose-proportional increase in systemic exposure in the dose range of 10 to 30 mg.

Co-administration of 30 mg in capsule formulation with a high-fat, high-calorie meal increases the plasma exposure (AUC) of avacopan by approximately 72% and delays t_{max} by approximately 3 hours; however, the C_{max} is not affected.

Distribution

The plasma protein binding (e.g., to albumin and α1-acid glycoprotein) of avacopan and metabolite M1 is greater than 99.9%. The apparent volume of distribution is high (Vz/F 3,000 – 11,000 L), indicating broad tissue distribution of the active substance.

Metabolism

Avacopan is eliminated mainly through phase I metabolism. Following oral administration of radiolabelled avacopan, the bulk of the active substance-related materials was recovered in faeces in the form of phase I metabolites. One major circulating metabolite (M1), a mono-hydroxylated product of avacopan, was present at ~12% of the total active substance-related materials in plasma. This metabolite constitutes 30 to 50% of the parent exposure and has approximately the same activity as avacopan on C5aR1. Cytochrome P450 (CYP) 3A4 is the major enzyme responsible for the clearance of avacopan and for the formation and clearance of the major circulating metabolite M1, a mono-hydroxylated product of avacopan.

Avacopan is a moderate inhibitor of CYP3A4 based on a 2.57-fold increase in the AUC of the probe active substance simvastatin in the presence of avacopan administered with food. A 1.81-fold increase in the AUC of midazolam was observed in the presence of avacopan administered in the fasted state. Avacopan is a weak inhibitor of CYP2C9 based on a 1.15-fold increase in the AUC of the probe active substance celecoxib in the presence of avacopan administered in the fasted state.

In vitro, avacopan is not an inhibitor or an inducer of other CYP enzymes.

Avacopan showed negligible to weak inhibition of common transporters *in vitro*. Therefore, clinically relevant interactions are unlikely when avacopan is co-administered with substances that are substrates or inhibitors of these transporters.

Excretion

Based on population pharmacokinetic analysis, the total apparent body clearance (CL/F) of avacopan is 16.3 L/h (95% CI: 13.1 – 21.1 L/h). The median terminal elimination half-life is 510 hours (21 days) based on population pharmacokinetic analysis. When avacopan is stopped after steady state has been reached, the residual plasma concentration of avacopan is projected to decrease to ~20%, <10%, and <5% of the steady state maximum concentration approximately 4 weeks, 7 weeks, and 10 weeks, respectively, after the last dose.

Following oral administration of radiolabelled avacopan, about 77% and 10% of the radioactivity was recovered in faeces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in faeces and urine, respectively. These results suggest that the main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into faeces, and that direct excretion of avacopan into urine or faeces via bile is negligible.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Avacopan was not mutagenic or clastogenic in *in vitro* bacterial reverse mutation test (Ames assay), *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus test.

Carcinogenicity

The carcinogenic potential of avacopan was evaluated in a 2-year study in both rats and hamsters.

Avacopan was not carcinogenic in hamsters, the pharmacologically relevant species, at oral doses of 100 mg/kg/day, equivalent to 4.4-fold the clinical AUC based on the combined exposures of avacopan and active metabolite M1. Avacopan demonstrated no tumorigenic potential in rats following oral doses up to 100 mg/kg/day (2.2-fold the clinical AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content:

- PEG-40 hydrogenated castor oil
- Macrogol 4000

Capsule shell

- Gelatin
- Iron oxide red
- Iron oxide yellow

- Titanium dioxide
- Polysorbate 80

Imprinting ink

- Iron oxide black
- Shellac
- Potassium hydroxide

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Store in the original bottle in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

High density polyethylene (HDPE) bottle with child-resistant closure and induction seal.

Pack sizes of 30 or 180 hard capsules.

Not all pack sizes may be marketed.

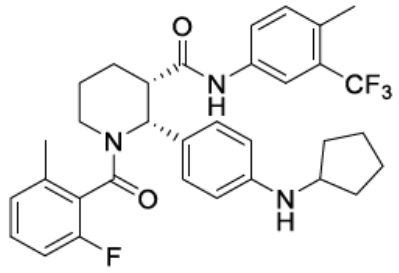
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

346623-17-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Seqirus Pty Ltd
63 Poplar Rd,
Parkville VIC 3052
Australia
1800 642 865 (Within Australia)

9 DATE OF FIRST APPROVAL

31 January 2023

10 DATE OF REVISION

25 August 2026

Summary table of changes

Section changed	Summary of new information
Boxed warning	Added Boxed Warning for serious hepatotoxicity, including vanishing bile duct syndrome

4.2	Addition of information on testing to be conducted prior to initiation of treatment and to advise when treatment with Tavneos should be discontinued, including if VBDS is suspected.
4.4	Further details added for ‘VBDS as a consequence of liver injury’ in the post-marketing setting. Instructions expanded for monitoring patients during treatment with Tavneos.
4.8	Correction to frequency of angioedema and added clarification to footnote (Table 2), with minor amendments to narrative for improved clarity.