PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**TAVNEOS®**

Avacopan

Capsules, 10 mg, Oral

Complement 5a receptor antagonist

Vifor Fresenius Medical Care Renal Pharma Ltd.
Rechenstrasse 37, 9014 St. Gallen
Switzerland

Imported by:
Otsuka Canada Pharmaceutical Inc.
Saint-Laurent, Quebec, H4S 2C9

Date of Initial Authorization:
April 14, 2022

Date of Revision:
April 19, 2022

Submission Control Number: 248255

RECENT MAJOR LABEL CHANGES

N/A

TABLE OF CONTENTS.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TAVNEOS (avacopan capsules) is indicated for:

- the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard background therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical trials suggest that use in geriatric population is not associated with a difference in effectiveness.

2 CONTRAINDICATIONS

TAVNEOS is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment with TAVNEOS should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of ANCA-associated vasculitis (GPA and MPA).

Serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin and Hepatitis B virus (HBV) serology should be obtained prior to initiating treatment with TAVNEOS to establish baseline liver function. For patients with evidence of prior or current HBV infection, consult with a physician with expertise in managing hepatitis B regarding monitoring and consideration for HBV treatment before or during treatment with TAVNEOS. TAVNEOS is not recommended for use in patients with cirrhosis, especially with severe hepatic impairment (Child-Pugh Class C) (see 6 WARNINGS AND PRECAUTIONS, Hepatic). Treatment with TAVNEOS should be re-assessed clinically if alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is more than 3 times the upper limit of normal.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of TAVNEOS is 30 mg (3 capsules of 10 mg each) taken orally twice daily with food.

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

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is > 3-5 × upper limit of normal (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.

Treatment may be resumed once drug-induced liver injury has been ruled out and upon normalization 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 any of the following occur:

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

Pediatric patients. Health Canada has not authorized an indication for pediatric use.

Patients with renal impairment. No dosage adjustment is required in patients with mild, moderate, or severe renal impairment. Avacopan has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Patients with hepatic impairment. Avacopan should be used with caution in patients with mild or moderate hepatic impairment. If a positive benefit-risk assessment is made, no dose adjustment is required in these patients. Avacopan has not been studied in patients with cirrhosis or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see 10.3 Pharmacokinetics: Special Populations and Conditions; Hepatic Insufficiency).

Geriatric patients. No dose adjustment is required in geriatric patients.

Patients taking strong CYP3A4 inhibitors. Reduce the dosage of TAVNEOS to 30 mg once daily when used concomitantly with strong CYP3A4 inhibitors (see 9.4 Drug-Drug Interactions).

Patients taking CYP3A4 substrates. Monitor for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with narrow therapeutic window (see 9.4 Drug-Drug Interactions).

4.4 Administration

TAVNEOS is for oral use.

The capsules should be taken with food in the morning and the evening.

The capsules should be swallowed whole with water and must not be crushed, chewed, or opened.

4.5 Missed Dose

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

5 OVERDOSAGE

TAVNEOS was studied in healthy subjects 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 management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: **Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule/10 mg of avacopan containing an opaque, white to slightly-coloured, waxy solid	Black iron oxide Gelatin Macrogol 4000 Macrogolglycerol hydroxystearate Polysorbate 80 Potassium hydroxide Red iron oxide Shellac Titanium dioxide Yellow iron oxide

TAVNEOS oral capsules have a light orange cap and yellow body with “CCX168” in black ink on the capsule.

Available in high density polyethylene (HDPE) bottle with child-resistant closure and induction seal. Bottles of 180 or 30 capsules.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

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. Certain treatment regimens may carry an increased risk for cardiac 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).

Gastrointestinal

TAVNEOS contains macrogolglycerol hydroxystearate as excipient, which may cause gastrointestinal symptoms such as dyspepsia, vomiting, nausea and diarrhoea. There was a case of serious nausea observed in the clinical trial.

Hepatic

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. In controlled clinical trials, the TAVNEOS treatment groups had a higher incidence of transaminases elevations and hepatobiliary events, including serious and life-threatening events (see 8 ADVERSE REACTIONS).

Obtain liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) before initiating treatment with TAVNEOS, and monitor every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If AST or ALT is > 3 times the upper limit of normal, temporarily stop TAVNEOS until TAVNEOS drug-induced liver injury is ruled out (see 8 ADVERSE REACTIONS); unless one of the situation of permanent discontinuations occurs (see 4.2 Recommended Dose and Dosage Adjustment).

TAVNEOS is not recommended for patients with activated, untreated and / or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administrating this drug to a patient with liver disease. Monitor patients closely for hepatic adverse reactions (see 7.1 Special Populations).

Immune

Angioedema

TAVNEOS may cause angioedema (see 8 ADVERSE REACTIONS). In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Immunization

The safety of immunization with live vaccines, following avacopan has not been studied. Administer vaccination preferably prior to initiation of treatment with avacopan.

Infection

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia (4.8%) and urinary tract infections (1.8%).

Avoid use of TAVNEOS in patients with an active serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS in patients:

- With chronic or recurrent infections
- Who have been exposed to tuberculosis
- With a history of a serious or an opportunistic infection
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- With underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection and treat accordingly. TAVNEOS may be resumed once the infection is controlled.

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.

Monitoring and Laboratory Tests

Liver function tests and Hepatitis B virus (HBV) serology should be obtained prior to initiation of therapy (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS, Hepatic). Patients should be monitored for elevation of liver function test periodically during the treatment with avacopan (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS).

Reproductive Health: Female and Male Potential

- **Fertility**

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

Fertility/early embryo development, embryo/foetal development, and pre- and post-natal development studies conducted with avacopan in hamsters or rabbits generally showed no evidence of reproductive toxicity or teratogenicity, at doses up to 1,000 mg/kg/day in hamsters and 200 mg/kg/day in rabbits; the only exceptions were an increased incidence of skeletal variations at 1,000 mg/kg/day avacopan in hamster and of abortion at 200 mg/kg/day avacopan in rabbits (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

Avacopan is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no data from the use of avacopan in pregnant women.

In animal studies designed to assess effects of avacopan upon embryo-fetal development with pregnant hamsters (dosed by the oral route during the period of organogenesis from gestation day 6 to 12), there was an increased incidence of skeletal variations (short thoracolumbar supernumerary rib) at the highest dose tested (500 mg/kg BID, which is equivalent to an exposure of 5 times the maximum recommended human dose calculated on an AUC basis with 1000 mg/kg/day). In a prenatal and postnatal development study with pregnant hamsters (orally dosed from gestation day 6 to lactation day 20), avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the maximum recommended human dose (based on maternal doses of up to 1000 mg/kg/day). An embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation day 6 to 18 was conducted. The study showed a dose-related increased incidence of abortion and early deliveries at an exposure 0.6 times the maximum recommended human dose (based on AUCs with the maternal oral doses of 30 mg/kg/day and higher) (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

The safety of avacopan when used during pregnancy or breastfeeding has not been evaluated in humans. There are no data on the use of avacopan in lactating women and it is unknown whether avacopan is excreted in human milk.

Avacopan has not been measured in milk of lactating animals; however, avacopan has been detected in the plasma of nursing animal offspring from drug-treated dams in a pre- and post-natal development study in hamsters at a pup to maternal plasma ratio of 0.37. The no-observed-adverse-effect-level (NOAEL) for viability, growth, and reproduction in F1 offspring was 1,000 mg/kg/day (500 mg/kg twice daily) (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue therapy with TAVNEOS, considering the benefit of breast-feeding for the child and the benefit of therapy for the woman suffering from ANCA-associated vasculitis.

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TAVNEOS in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No dosage adjustments are required in patients aged 65 years of age and older (see 10 CLINICAL PHARMACOLOGY and 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of TAVNEOS has been studied in two (2) Phase 2 clinical trials and one (1) Phase 3 clinical trial (ADVOCATE) involving 239 subjects with ANCA-associated vasculitis who received at least one dose of TAVNEOS.

The frequencies of adverse reactions are those reported in the Phase 3 trial (n = 330); a prospective, randomized, double-blind, double-dummy, active-controlled clinical trial assessing TAVNEOS (30 mg TAVNEOS twice a day for 52 weeks) in subjects with newly diagnosed or relapsing active ANCA-associated vasculitis when administered with a standard background cyclophosphamide or rituximab regimen: 166 subjects were in the TAVNEOS group and 164 subjects were in the prednisone group.

The most common adverse reactions in subjects with ANCA-associated vasculitis who received TAVNEOS plus cyclophosphamide or azathioprine or mycophenolate mofetil or rituximab, were headache (20.5%), nausea (23.5%) and vomiting (15.1%). Only one nausea treatment-emergent adverse event (TEAE) was considered serious, and none of the vomiting and headache events were considered serious. Serious adverse reactions reported more frequently in patients with TAVNEOS than the comparator treatment groups were pneumonia (4.8% vs 3.7%), urinary tract infection (1.8% versus 1.2%) and hepatic function abnormal (1.2% vs 0.0%).

Severe adverse reactions reported more frequently in patients with TAVNEOS than the comparator treatment groups and in ≥ 1% of patients were pneumonia (2.4% vs. 1.2%) and hepatic function abnormal (1.2% vs. 0%).

Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the shorter duration phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. The most frequent adverse reactions that led to drug discontinuation reported by ≥ 1 patient and more frequently in patients treated with TAVNEOS was hepatic function abnormality (1.8%).

In the pivotal phase 3 trial, 2 subjects (1.2%) in the TAVNEOS group had a TEAE of angioedema. One subject was hospitalized for the event. TAVNEOS treatment was discontinued, and angioedema did not recur.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying and approximating rates of adverse drug-related reactions in real-world use.

Table 2: Adverse Reactions with Incidence of ≥5% in Subjects who Received TAVNEOS in the ANCA-Associated Vasculitis Phase 3 Trial

System Organ Class MedDRA Preferred Term	TAVNEOS (N = 166) n (%)	PREDNISONE (N = 164) n (%)
Gastrointestinal Disorders		
nausea	39 (24%)	34 (21%)
vomiting	25 (15%)	21 (13%)
diarrhea	25 (15%)	24 (15%)
abdominal pain upper	11 (7%)	10 (6%)
General Disorders and Administration Site Conditions		
fatigue	17 (10%)	15 (9%)
Infections and Infestations		
nasopharyngitis	25 (15%)	30 (18%)
upper respiratory tract infection	24 (15%)	24 (15%)
urinary tract infection	12 (7%)	23 (14%)
pneumonia	11 (7%)	11 (7%)
sinusitis	10 (6%)	12 (7%)
Nervous system Disorders		
headache	34 (21%)	23 (14%)
Skin and Subcutaneous Tissue Disorders		
rash	19 (11%)	13 (8%)
Vascular Disorders		
hypertension	30 (18%)	29 (18%)

8.3 Less Common Clinical Trial Adverse Reactions

Immune: *Hypersensitivity including Angioedema* - In the pivotal phase 3 trial, 2 subjects (1.2%) in the TAVNEOS group had a TEAE of angioedema. One subject was hospitalized for the event. TAVNEOS treatment was discontinued and both events resolved without sequelae. TAVNEOS was restarted in 1 subject and angioedema did not recur.

Infections and infestations: bronchitis, cellulitis, gastroenteritis, herpes zoster, influenza, lower respiratory tract infection, oral candidiasis, oral herpes, otitis media, rhinitis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry And Other Quantitative Data

Table 3: Hematologic

System Organ Class MedDRA Preferred Term	TAVNEOS (N = 166) n (%)	PREDNISONE (N = 164) n (%)
Blood and lymphatic system disorders		
neutropenia	4 (2%)	4 (2%)
Investigations		
white blood cell count decreased*	8 (5%)	2 (1%)
* Includes leukopenia.		

Table 4: Clinical Chemistry

System Organ Class MedDRA Preferred Term	TAVNEOS (N = 166) n (%)	PREDNISONE (N = 164) n (%)
Hepatobiliary disorders		
liver function test increased*	22 (13%)	19 (12%)
ALT increase >3-5 ULN	6 (4%)	4 (2%)
AST increase >3-5 ULN	3 (2%)	0
Bilirubin increase >1.5-3 ULN	2 (1%)	1 (1%)
Bilirubin increase >3-10 ULN	1 (1%)	0
Investigations		
blood creatine phosphokinase increased	6 (4%)	1 (1%)
* Alanine aminotransferase increased, total blood bilirubin increased, hepatic function abnormal, gamma glutamyl transferase increased, hepatic enzyme increased, transaminases increased.		

Liver function test increased

Elevations (>3 to 5 x ULN) of ALT were observed in 3.6% (6/166) of subjects treated with TAVNEOS, and 2.4% (4/164) of subjects treated with prednisone during the 52 weeks of the Phase 3 clinical trial, while elevations (>3 to 5 x ULN) of AST were observed in 1.8% (3/166) of subjects treated with TAVNEOS and 0% (0/164) subjects treated with prednisone (see 7 WARNINGS AND PRECAUTIONS, Hepatic). Elevations (>1.5 to 3 x ULN) of bilirubin were observed in 1.2% (2/166) of subjects treated with TAVNEOS, and 0.6% (1/164) of subjects treated with prednisone. Elevation (>3 to 10 x ULN) of bilirubin was only observed in one subject (0.6%) treated with TAVNEOS and no subjects treated with prednisone.

Blood Creatine phosphokinase increased

Increased blood creatine phosphokinase (CPK) TEAEs were reported in 6 subjects (3.6%) in the TAVNEOS group and 1 subject (0.6%) in the prednisone group in the Phase 3 trial. One TAVNEOS treated patient discontinued treatment due to increased creatinine phosphokinase. No increases in blood CPK were reported in either treatment group as an SAE. No adverse events of rhabdomyolysis were observed.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Avacopan is a substrate of cytochrome P450 (CYP) 3A4 and thus co-administration with CYP3A4 inhibitors or CYP3A4 inducers may lead to a change in avacopan exposure (see 4.1 Dosing Considerations).

9.3 Drug-Behavioural Interactions

Consumption of alcohol could exacerbate ALT and AST elevations and should be minimized when avacopan is being taken.

9.4 Drug-Drug Interactions

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

In vitro studies indicate that avacopan is not a substrate of BCRP (Breast cancer resistance protein) and P-gp (p-glycoprotein) efflux, or of OATP1B1 (Organic anion transporting polypeptide 1B1) and OATP1B3 (Organic anion transporting polypeptide 1B3) uptake transporters. M1, avacopan's major metabolite, is a substrate of P-gp but is not a substrate of BCRP efflux, or of OAT1B1 and OATP1B3 uptake transporters.

Effect of Other Drugs on Avacopan

Effect of strong CYP3A4 inducers on avacopan

Co-administration of avacopan with rifampicin (600 mg, once daily, 11 days), 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, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with avacopan should be avoided. Patients anticipated to require long term administration of these active substances should not be treated with avacopan. If short-term co-administration cannot be avoided in a patient already using avacopan, the patient should be monitored closely for recurrence of disease activity (see 4.1 Dosing Considerations).

Effect of moderate CYP3A4 inducers on avacopan

Concomitant use of moderate inducers (e.g., bosentan, efavirenz, etravirine, and modafinil) should be avoided. If co-administration cannot be avoided in a patient already using TAVNEOS, the patient should be monitored closely for recurrence of disease activity.

Effect of strong CYP3A4 inhibitors on avacopan

Co-administration of avacopan with itraconazole (200 mg, once daily, 4 days), a strong CYP3A4 enzyme inhibitor, resulted in an increase in AUC and C_{max} of avacopan by approximately 119% and 87%, respectively. Therefore, concomitant use of avacopan with strong CYP3A4 enzyme inhibitors (e.g.,

boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) should be used with caution in patients who are being treated with avacopan. Administer TAVNEOS 30 mg once daily when co-administered with strong CYP3A4 inhibitors (see 4.1 Dosing Considerations, 4.2 Recommended Dose and Dosage Adjustment).

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 Other Drugs

Effect of avacopan on CYP3A4 and CYP2C9 substrates

In a human drug-drug interaction study, avacopan was a weak inhibitor of CYP3A4 and CYP2C9 when administered at a dose of 30 mg twice daily on Days 3 to 19, as indicated by an increase of approximately 81% and 15% in the AUC of the probe drugs midazolam and celecoxib, respectively. Monitor for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with narrow therapeutic window. See 4.2 Recommended Dose and Dosage Adjustment.

Effect of avacopan on other CYP substrates

In vitro, avacopan was shown to not be an inhibitor or inducer of other CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CP2C9, CYP2C19, CYP2D6). Co-administration of avacopan with substrates of other CYP enzymes is, therefore, unlikely to significantly affect the clearance and the exposure of active substances that are metabolized by CYP enzymes and no dose adjustment of CYP enzyme substrates is required.

Effect of avacopan on Transporters

Avacopan showed negligible to weak inhibition of the following transporters: P-gp, BCRP, OATP1B1, OATP1B3, OAT1 (Organic anion transporter 1), OAT3 (Organic anion transporter 3), OCT2 (Organic cation transporter 2), MATE1 (Multidrug and toxin extrusion 1) and MATE2-K (Multidrug and toxin extrusion 2) *in vitro*. Therefore, clinically relevant drug-drug interactions are unlikely when avacopan is co-administered with substances that are substrates or inhibitors of these transporters.

9.5 Drug-Food Interactions

Grapefruit and grapefruit juice can increase the concentration of avacopan; therefore, grapefruit and grapefruit juice should be used with caution in treated patients with avacopan.

Avacopan should be taken with food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established; however, St John's Wort should be avoided while taking TAVNEOS.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Avacopan is a small molecule C5a receptor antagonist that selectively blocks the effect of C5a through the receptor (C5aR1 or CD88), including blocking neutrophil chemoattraction and activation. It competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a.

C5a and C5aR1 play a central role in the pathogenesis of ANCA-associated vasculitis (AAV). C5a is released when neutrophils are stimulated by inflammatory cytokines and C5a primes and activates further neutrophils. C5a is a powerful neutrophil chemoattractant and increases neutrophil adhesion and decreases their deformability. C5a also activates vascular endothelial cells, promoting their retraction and increased permeability. The interaction between neutrophils and C5a generated through activation of the alternative complement pathway is critical to vascular inflammation and organ damage in AAV.

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

Avacopan does not inhibit the formation of the membrane attack complex (MAC; composed of complement fragments C5b, C6, C7, C8 and C9) or terminal complement complex (TCC), which is important in fighting infections with encapsulated bacteria such as *Neisseria meningitidis*.

10.2 Pharmacodynamics

Avacopan reduced the severity of disease in a 6-day study in ANCA-induced glomerulonephritis model in human C5aR transgenic mice. Both 5 mg/kg twice-daily (BID) avacopan-treated mice and 37.5 mg/kg once-a-day (QD) avacopan-treated mice exhibited significant reductions in the incidence of histologically evident glomerular crescent formation and necrosis, the primary hallmarks of disease, relative to vehicle-treated mice. In addition, both 5 mg/kg BID avacopan-treated mice and 37.5 mg/kg QD avacopan-treated mice exhibited significantly reduced indicators of kidney dysfunction, including proteinuria, leukocyturia, and hematuria.

The effect on neutrophil migration was studied in healthy subjects receiving single 30 mg or 100 mg daily doses of avacopan; however, ex vivo inhibition of chemotaxis was determined to not be a reliable metric for measuring avacopan inhibition of C5aR in this study.

The effect of avacopan on C5a-induced CD11b upregulation was studied in healthy subjects receiving single 10 mg, 30 mg, and 100 mg daily doses and 30 mg twice-daily doses of avacopan. CD11b expression was used as a surrogate endpoint for inhibition of C5aR because it is a downstream target of C5a-C5aR signaling. CD11b upregulation was measured by fluorescence activated cell sorting (FACS) at 2 hours and 12 or 24 hours post-dose. The CD11b upregulation study provided preliminary evidence that blood neutrophils from subjects treated with a single dose of avacopan, but not placebo-treated subjects, were impaired in their ability to upregulate CD11b in response to exogenously-added recombinant C5a. In the 30 mg avacopan BID group, the overall expression levels of CD11b were higher than in the single dose groups, and the trend of CD11b inhibition was less pronounced.

Avacopan functionally inhibited C5a-mediated chemotaxis *in vitro* using a myeloid human cell line with potency (IC_{50}) of 0.92 nM. Additionally, avacopan displaced ^{125}I-C5a from human C5aR with an IC_{50} of

0.45 nM. When tested on freshly isolated human neutrophils, avacopan inhibited the C5a-mediated increase in cytoplasmic calcium levels with an IC_{50} of 0.2 nM.

The effects of therapeutic (30 mg BID) and supratherapeutic doses (100 mg BID) of avacopan on the heart rate corrected QT interval was evaluated in a thorough QT study in healthy subjects. Avacopan at the studied doses had no clinically relevant effects on cardiac repolarization, i.e., QT/QTc intervals, or on cardiac conduction, i.e., the PR and QRS intervals. Based on the concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded within the full observed range of plasma concentrations of avacopan and the primary metabolite (M1), up to ~1220 ng/mL and ~335 ng/mL, respectively. The C_{max} values (mean value of 819.2 ng/mL with a maximum of 1220 ng/mL) on Day 14 of this study following 100 mg BID for 7 days are over twice the steady state C_{max} value (349 ng/mL) predicted by population PK modeling in subjects with ANCA-associated vasculitis receiving 30 mg BID.

10.3 Pharmacokinetics

Avacopan exhibits linear pharmacokinetics (PK). In patients with ANCA-associated vasculitis receiving 30 mg avacopan twice daily, based on population PK analysis, the area under the plasma concentration over time curve ($AUC_{0\text{-}12hr}$) and maximum plasma concentration (C_{max}) were estimated to be 3466 ± 1921 ng*h/mL and 349 ± 169 ng/mL, respectively. Following administration of avacopan at 30 mg BID in subjects with ANCA-associated vasculitis, the steady state of avacopan plasma levels were reached by Week 13 with a 4-fold accumulation, estimated by population PK analysis.

Absorption

Following single oral doses of 1 mg to 100 mg QD without food in healthy subjects, avacopan was rapidly absorbed, with a T_{max} at 1 to 2.5 hours, and the plasma exposures of avacopan increased approximately dose-proportionally for C_{max} (1 – 100 mg) and AUC (30 – 100 mg). Approximately dose-proportional exposures were also observed upon multiple dosing of avacopan in the range of 10 mg to 100 mg.

At least 93% of the oral dose was absorbed following an oral solution dose of 100 mg avacopan.

Administration of avacopan to subjects on a high fat, high calorie meal led to an increased AUC (fed/fasted AUC ratio = 1.72) and a delayed absorption (mean T_{max} increased by ~ 3 hours), but the C_{max} remained unchanged.

Distribution:

Tissue distribution of avacopan is extensive with a mean Vz/F value in the range of approximately 3,000 to 11,000 L after a single dose of 30 mg avacopan in healthy subjects.

Avacopan and the mono-hydroxylated CCX168-M1 (M1) metabolite are reversibly protein bound in human plasma at >99.9% over the concentration range of 2.5 to 50 µM. Avacopan is bound reversibly to human albumin and α1-acid glycoprotein (AAG) at >99.9%, while M1 is bound reversibly to human albumin and AAG at 99.9% and ~99%, respectively.

Metabolism:

Avacopan is metabolized by CYP3A4-mediated oxidation. There is one major circulating metabolite, mono-hydroxylated CCX168-M1 (M1), which is present at approximately 12% of the total plasma exposure. This metabolite constitutes 30 to 50% of the parent exposure has approximately the same activity as avacopan on the C5aR.

Avacopan and the primary metabolite M1 displayed negligible direct inhibition of CYP enzymes except

for M1 being identified as a weak inhibitor of CYP2C9 (IC_{50} = 4.7 µM). In human liver microsomes, both avacopan and M1 showed no time-dependent inhibition against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 but displayed some degree of time-dependent inhibition of CYP3A4.

Elimination

The main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into faeces. 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.

Based on population PK analysis, the total apparent body clearance (CL/F) of avacopan is 16.3 ± 2.05 L/h (95% CI: 13.1 - 21.1 L/h). The mean effective half-life is 38.8 ± 19.0 hours and the median terminal elimination half-life is 545 ± 199 hours. 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.

Special Populations and Conditions

Pediatrics: The safety and efficacy of TAVNEOS have not been established in children.

Geriatrics: Population PK analysis found no significant effect of age (among adults) on the plasma exposure of avacopan; however, there were limited (PK) data in subjects over 75 years of age in clinical trials. No dosage adjustment is necessary for geriatric patients.

Hepatic Insufficiency: The PK properties of avacopan have been examined in 16 subjects 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 of avacopan or its major metabolite M1 were observed (geometric mean ratios for both the C_{max} and AUC_{last} were within the range of 0.8 – 1.25). Compared to subjects with normal liver function, in subjects with mild or moderate hepatic impairment, avacopan AUC increased by 12% and 12%, respectively, avacopan C_{max} decreased by 13% and 17%, respectively, M1 AUC increased by 11% and 18%, respectively, and M1 C_{max} decreased by 5% and 16%, respectively. Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

Renal Insufficiency: The Phase 3 trial included ANCA-associated vasculitis subjects with various degrees of renal impairment (severe: eGFR <30 mL/min/1.73 m^2; moderate: 30 – 60 mL/min/1.73 m^2; normal or mild: >60 mL/min/1.73 m^2). Population PK analysis of these subjects found that renal function (eGFR) is a covariate of avacopan PK. Moderate and severe renal impairment decreased the clearance of avacopan by 15 – 34% and 34 – 49%, respectively. The majority of subjects (>85%) with ANCA-associated vasculitis in the Phase 3 trial had mild to severe renal impairment. The steady state mean plasma exposures (AUC, C_{max} or C_{min}) of avacopan or the metabolite M1 were similar (<20%) among these subjects with renal impairment based on the population PK analysis. A small percentage of the subjects in the Phase 3 trial had normal renal function and their avacopan exposures were slightly lower but still within 25% compared to average values in subjects with renal impairment. Avacopan has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 °C to 30 °C) and in the original package. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

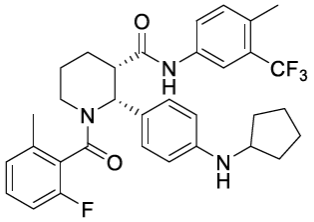
Drug Substance

Proper name: avacopan

Chemical name: 3-piperidinecarboxamide, 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-, *(2R,3S)*-

Molecular formula and molecular mass: $C_{33}H_{35}F_4N_3O_2$ 582 Da.

Structural formula:



Physicochemical properties: Avacopan is white to pale yellow solid. It is practically insoluble in aqueous media (<0.011 mg/mL) and no pH dependence of solubility was observed.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

TAVNEOS (avacopan capsules) is indicated for:

- the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard background therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

The trial design is summarised below in Table 5:

Table 5: **Summary of Subject Demographics for the Phase 3 Clinical Trial (ADVOCATE) in ANCA-Associated Vasculitis**

Trial #	Trial design	Dosage, route of administration and duration	Trial subjects (n)	Mean age (Range)	Sex
CL010_168 (ADVOCATE)	Phase 3, randomized, double-blind, double-dummy, active-controlled trial	3 x 10 mg oral capsules, twice daily, 52 weeks +8 weeks follow-up	Avacopan (166) Prednisone (165)	64 (13-88 years)	187 males (56.5%) 144 females (43.5%)

The pivotal Phase 3 trial (ADVOCATE) was a randomised, double-blind, double-dummy, active-controlled clinical trial, assessing the efficacy, safety, and tolerability of avacopan in subjects with newly diagnosed or relapsing active ANCA-associated vasculitis when administered against a standard background cyclophosphamide or rituximab regimen. The trial treatment period was 52 weeks with an 8-week follow-up period.

The primary objectives of the trial were to evaluate the efficacy of avacopan to achieve:

- Remission at week 26; defined as Birmingham Vasculitis Activity Score (BVAS)=0 and not taking glucocorticoids for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis within 4 weeks before week 26
- Sustained remission at week 52; defined as remission at week 26 and week 52, without relapse through week 52, and not taking glucocorticoids for ANCA-associated vasculitis within 4 weeks before week 52

The inclusion criteria included subjects with GPA and MPA and subjects with renal or non-renal vasculitis.

A total of 331 subjects were randomised in a 1:1 ratio to one of two treatment groups:

- TAVNEOS group (N=166): Subjects received 30 mg TAVNEOS twice daily for 52 weeks plus prednisone-matching placebo tapering regimen over 20 weeks
- Prednisone group (N=164): Subjects received TAVNEOS-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:

- IV 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), or
- Oral cyclophosphamide for 14 weeks (2 mg/kg daily) followed by oral azathioprine, or mycophenolate mofetil starting at week 15 (same dosing regimen as IV cyclophosphamide) or
- Rituximab at the dose of 375 mg/m² for 4 weekly IV doses.

Subjects were stratified at time of randomization based on three factors:

- Receiving either intravenous (IV) rituximab, IV cyclophosphamide, or oral cyclophosphamide
- Having proteinase 3 (PR3) or myeloperoxidase (MPO) ANCAs
- Newly diagnosed or relapsed ANCA-associated vasculitis.

Table 6: Selected baseline characteristics in the pivotal phase 3 ADVOCATE trial (Intent-to-Treat Population)

Demographic characteristic	TAVNEOS (N=166)	Prednisone tapering arm (N=164)
ANCA-associated vasculitis Status, n (%)		
Newly diagnosed	115 (69.3%)	114 (69.5%)
Relapsed	51 (30.7%)	50 (30.5%)
Gender, n (%)		

Male	98 (59.0%)	88 (53.7%)
Female	68 (41.0%)	76 (46.3%)
Background treatment, n (%)		
Rituximab	107 (64.5%)	107 (65.2%)
IV or Oral cyclophosphamide	59 (35.5%)	57 (34.8%)
ANCA Positivity, n (%)		
PR3	72 (43.4%)	70 (42.7%)
MPO	94 (56.6%)	94 (57.3%)
Type of ANCA-associated vasculitis, n (%)		
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 (MDRD)		
Mean ± SEM	44.6 ± 2.42	45.6 ± 2.36
Glucocorticoid		
Subjects with prior glucocorticoid use	125 (75.3%)	135 (82.3%)

Abbreviations: ANCA=antineutrophil cytoplasmic autoantibody; BVAS= Birmingham Vasculitis Activity Score; IV=intravenous; MDRD: Modified Diet in Renal Disease; MPO=myeloperoxidase; PR3=proteinase-3; SEM: Standard error of mean.

Disease Remission and Sustained Remission

As shown in Table 7, the trial met both of its primary endpoints, remission at Week 26 and sustained remission at Week 52. The avacopan group was not inferior to the prednisone group with respect to the proportion of subjects who achieved disease remission at Week 26 and was superior with regard to those who achieved sustained remission at Week 52.

Table 7: **Results of the Phase 3 Trial (ADVOCATE) in ANCA-Associated Vasculitis (Intent-to-Treat Population)**

Primary Endpoints	n/N (%)		P-value
	Avacopan	Prednisone tapering arm	
Disease Remission at Week 26	120/166 (72.3%)	115/164 (70.1%)	<0.0001 (non-inferiority) 0.2387 (superiority)
Sustained Remission at Week 52	109/166 (65.7%)	90/164 (54.9%)	<0.0001 (non-inferiority) 0.0066 (superiority)

Abbreviations: N=number of subjects in the analysis population for the treatment group; n=number of subjects with disease remission

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Avacopan and metabolite M1 were found to be potent antagonists of human, hamster, and monkey C5aR, moderately potent against rabbit C5aR, but to be non- or minimally active against rat and mouse C5aR. Therefore, rat and mouse (excluding human C5aR transgenic mice, see 10.2 Pharmacodynamics) are not considered a pharmacologically relevant species.

Single-Dose Toxicity

A single-dose oral (gavage) toxicity study was conducted in male and female young adult Sprague Dawley rats at doses up to 100 mg/kg. There were no clinical observations attributable to avacopan and no effects upon body weight or food consumption from avacopan treatment. There were no statistically significant avacopan-related changes in hematology, clinical chemistry and urinalysis parameters. There were no avacopan-related gross macroscopic lesions or microscopic liver findings. No changes in organ weights attributed to treatment with avacopan were noted. Based on these results the No Observed Adverse Effect Level (NOAEL) was determined to be ≥ 100 mg/kg.

Repeat-Dose Toxicity

In 13-week and 26-week repeat-dose toxicity studies in rats, avacopan was well tolerated at doses up to 100 mg/kg/day and 200 mg/kg/day, respectively. There was no avacopan-related mortality during either study. The only avacopan-related clinical observation was infrequent salivation (considered non-adverse and noted only in the 13-week study) which was noted in the mid- and high-dose groups. There were no avacopan-related changes in body weights, food consumption, ophthalmic examinations, gross observations, organ weights, or histopathology. Clinical pathology changes were limited to minor serum chemistry changes in the 26-week study at doses >100 mg/kg/day which were small in magnitude, reversible, and considered non-adverse. The NOAEL for avacopan in the 13-week and 26-week studies was determined to be 100 mg/kg/day and 200 mg/kg/day (the highest doses

assessed), respectively.

In 20-week and 44-week repeat-dose toxicity studies in cynomolgus monkeys, avacopan was well tolerated at doses up to 30 mg/kg/day and 30/45 mg/kg/day, respectively. As a result of a dosing modification in the 44-week study, animals received either 0 (vehicle control article), 5, 15, or 30 mg/kg/day of avacopan from Weeks 1 to 25, and then 0, 7.25, 22.5, or 45 mg/kg/day of avacopan from Weeks 26 to 44. Once daily dosing was via nasogastric intubation (Weeks 1-5), and via oral gavage thereafter. There was no mortality observed during either study. There were no avacopan-related changes in clinical observations, body weights, ophthalmic examinations, electrocardiographic examinations, neurological evaluations, blood pressure and respiratory examinations, immunotoxicology endpoints, clinical pathology gross observations, organ weights, or histopathology. The NOAEL in the 20-week and 44-week studies was determined to be 30 mg/kg/day and 30/45 mg/kg/day, respectively.

Carcinogenicity

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

Avacopan was not carcinogenic in female rats at all doses up to and including 100 mg/kg/day (the highest dose tested). In male rats, there was an increased incidence in c-cell adenomas with an incidence of 13/57 (23%) at 100 mg/kg/day; this increase was not statistically significant and the incidence was within the historical control range. There was an increase in non-neoplastic focal C-cell hyperplasia in the thyroid of male rats, with highest incidence (11/57 or 19.3%) at 100 mg/kg/day, which was within the historical range.

Avacopan was not carcinogenic in hamsters, the pharmacologically relevant species.

Genotoxicity

The genotoxic potential of avacopan was assessed in a battery of *in vitro* and *in vivo* test systems. In the bacterial reverse mutation (Ames test) assay, avacopan did not cause an increase in the mean number of revertants per plate with any tester strains, either in the presence or absence of microsomal activation (S9 fraction) prepared from Aroclor™-induced rat liver. Avacopan was found to be negative for inducing forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells, under the metabolic activation and non-activation conditions used for this assay. Similarly, avacopan was negative in the rat bone marrow micronucleus assay, following two consecutive daily oral doses up to the dose limit of 2,000 mg/kg/day. Based upon *in vitro* and *in vivo* metabolism data, the genetic toxicity studies characterized the effects of not only avacopan, but also the metabolite M1.

Reproductive and Developmental Toxicology

In a hamster fertility and early embryo development study (Segment I), avacopan at oral doses of up to 1,000 mg/kg/day (500 mg/kg BID) produced no effects on male or female fertility.

In a hamster embryo-fetal development study (Segment II), oral doses of up to 1,000 mg/kg/day (500 mg/kg BID) avacopan were given from gestation day (GD) 6 to 12. An increased incidence of skeletal variations (short thoracolumbar supernumerary rib) was observed at 1,000 mg/kg/day (500 mg/kg BID). No other adverse gross external, soft tissue or skeletal fetal abnormalities were associated with either daily doses up to 100 mg/kg or twice daily doses of 500 mg/kg avacopan in hamsters.

In a rabbit embryo-fetal development study (Segment II), oral doses of up to 200 mg/kg/day avacopan were given from GD 6 to 18 (during the period of organogenesis). No avacopan-related gross external, soft tissue or skeletal fetal alterations (malformations or variations) were observed at doses as high as

200 mg/kg/day. There was a dose-related increase in spontaneous abortions or early deliveries due to maternal toxicity. The maternal NOAEL was 30 mg/kg/day. The developmental NOAEL was 200 mg/kg/day.

A pre- and post-natal development study (Segment III) in hamsters, with avacopan given as daily doses up to 100 mg/kg or BID doses of 500 mg/kg from GD 6 through lactation until weaning of the offspring, resulted in no adverse findings in either the F0 dams or the F1 offspring, including developmental, behavioral, immunological or reproductive measures. The NOAEL for reproduction in the dams, and for viability, growth, and reproduction in the F1 generation hamsters was 1,000 mg/kg/day (500 mg/kg BID). Systemic exposure to avacopan and metabolite M1 (C_{max} hours and $AUC_{0\text{-}8hr}$) increased with the increase in avacopan dose level from 10 to 100 mg/kg/day but did not increase at 1,000 mg/kg/day. Analysis of avacopan plasma levels in the lactating dams and the plasma levels in nursing offspring on the 15th day of lactation showed the presence of avacopan. Thus, avacopan is likely excreted into the milk of lactating hamsters.

Special Toxicology

Phototoxicity

Avacopan absorbs light between 290 nm and 370 nm, with a peak molar extinction coefficient of 2989 L mol^{-1} cm^{-1} at 290 nm. An *in vitro* study in Balb/c 3T3 mouse fibroblasts revealed that avacopan was not phototoxic when tested up to the solubility limit (10 µM) in culture media.

Immunotoxicity

No evidence of avacopan-related inhibition of T-cell dependent humoral responses related to C5aR inhibition was seen in a 4-week T-cell dependent antibody response (TDAR) study in rats when avacopan was administered orally at doses up to 100 mg/kg/day. No effects upon immunophenotypic parameters or TDAR were observed in a 44-week repeat-dose toxicity studies in cynomolgus monkeys.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTAVNEOS®

Avacopan oral capsule

Read this carefully before you start taking TAVNEOS and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TAVNEOS.

What is TAVNEOS used for?

TAVNEOS is used to treat adults with conditions known as severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

- These include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).
- TAVNEOS is used along with other medicines to treat your condition.

How does TAVNEOS work?

TAVNEOS binds to a receptor in the body and blocks inflammation. This can be detected within hours. Your symptoms may improve within the first 4 weeks.

What are the ingredients in TAVNEOS?

Medicinal ingredient: avacopan

Non-medicinal ingredients: black iron oxide, gelatin, macrogol 4000, macrogolglycerol hydroxystearate, polysorbate 80, potassium hydroxide, red iron oxide, shellac, titanium dioxide, yellow iron oxide

TAVNEOS comes in the following dosage forms:

As 10 mg capsules.

Do not use TAVNEOS if:

- You are allergic to avacopan or to any of the ingredients in TAVNEOS (see What are the ingredients in TAVNEOS).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAVNEOS. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- have hepatitis B virus (HBV) infection.
- are pregnant, think you might be pregnant or are planning to become pregnant. It is not known if TAVNEOS may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TAVNEOS can pass into your milk and harm your baby. Talk to your healthcare professional about the best way to feed your baby if you take TAVNEOS.
- have an infection or infections that often come back.
- have heart problems.
- are planning to receive a vaccine. It is recommended that you receive vaccinations before starting treatment with TAVNEOS.

- are taking the medicines cyclophosphamide and azathioprine

Other warnings you should know about:

Liver problems: Serious liver problems have happened to patients taking TAVNEOS. Your healthcare professional will monitor your liver function before you start TAVNEOS and while you are taking it. They might decide to stop treatment based on these test results. Talk to your healthcare professional if you get any symptoms of liver problems. These include: yellow skin or whites of eyes, nausea, tiredness or feeling unwell, loss of appetite, fever, skin rash, abdominal pain, pale stool or dark coloured urine.

Angioedema (Serious swelling under the skin): TAVNEOS can cause a serious reaction called angioedema. See "Serious side effects and what to do about them" for symptoms and what to do if you get them.

Infections: Serious infections can happen in people taking TAVNEOS and these infections can lead to death. The most common serious infections were pneumonia and urinary tract infections. Other infections can also happen. See "Serious side effects and what to do about them" for symptoms and what to do if you get them. Your healthcare professional will monitor you for infections while you are taking TAVNEOS. They might stop and restart your treatment. It is recommended that you have treatment to prevent the lung infection *Pneumocystis jirovecii* pneumonia during treatment with TAVNEOS.

Hepatitis B virus reactivation: Before you take TAVNEOS, your healthcare provider will do blood tests to check for hepatitis B infection. If you have HBV infection, TAVNEOS could cause you to have an active infection again. Your healthcare professional will monitor your HBV infection during treatment with TAVNEOS. Talk to your healthcare professional if you get any of the following symptoms: fever, tiredness, yellow skin or to the whites of eyes, abdominal pain, diarrhea.

Macrogolglycerol hydroxystearate: TAVNEOS contains macrogolglycerol hydroxystearate as a non-medicinal ingredient. This may cause stomach upset, diarrhea, vomiting and nausea.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TAVNEOS:

- boceprevir, telaprevir, used to treat hepatitis C infection
- bosentan, used to treat high blood pressure in the lungs, and certain skin hardening or abscesses
- carbamazepine and phenytoin, used to treat epilepsy and other illnesses
- clarithromycin and telithromycin, used to treat bacterial infections
- conivaptan, used to treat low blood sodium levels
- enzalutamide and mitotane: medicines to treat cancer
- indinavir, efavirenz, etravirine, lopinavir, nelfinavir, ritonavir and saquinavir, used to treat HIV infections
- itraconazole, ketoconazole, posaconazole and voriconazole, used to treat fungal infections
- mibefradil, used to treat irregular heart rhythm and high blood pressure
- modafinil, used to treat an extreme tendency to fall asleep
- nefazodone and St. John's Wort, used to treat depression
- phenobarbital, used to treat epilepsy
- rifampicin, used to treat tuberculosis or certain other infections

Grapefruit and grapefruit juice are not recommended during treatment with TAVNEOS, as they can influence the effect of the medicine.

Drinking alcohol while taking TAVNEOS can change the way your liver works. Talk to your healthcare professional about limiting your alcohol intake.

How to take TAVNEOS:

- Take TAVNEOS exactly as your healthcare professional tells you to.
- It will be prescribed to you by a healthcare professional with experience in the diagnosis and treatment of GPA and MPA.
- Take TAVNEOS with food.
- Swallow the capsules whole with water. Do not crush, chew or open the capsules.
- Check with your healthcare professional if you are not sure how to take TAVNEOS.

Usual dose:

Adult: Take 3 capsules with food in the morning and 3 capsules with food in the evening.

Overdose:

If you think you, or a person you are caring for, have taken too much TAVNEOS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take the missed dose as soon as you remember. However, do not take the missed dose if it is within 3 hours to your next dose. Never take two doses at the same time.

What are possible side effects from using TAVNEOS?

These are not all the possible side effects you may have when taking TAVNEOS. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- high blood pressure, fatigue
- nausea, vomiting, diarrhea, pain in the belly
- headache
- rash
- flu, cold
- cold sore
- gastroenteritis (stomach flu)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Increased levels of a blood enzyme (creatine phosphokinase): cramps, muscle pain, tenderness and stiffness.		**X**	
Infection of the respiratory system, mouth, skin or ear: fever, chills, sore throat that does not go away, white patches in your mouth, pain when swallowing, cough, stuffy nose that does not go away, pain or pressure in your face, fatigue, body aches, earache, headache, red, swollen, painful or itchy areas of the skin, rash, numbness or tingling of your skin, skin blisters.		**X**	
Liver problems: yellow skin or to the whites of eyes, nausea, tiredness or feeling unwell, loss of appetite, fever, skin rash, abdominal pain, pale stool or dark coloured urine.		**X**	
Pneumonia (infection of the lungs): cough with or without mucus, fever, chills, shortness of breath.		**X**	
Urinary tract infection: Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine, fever.		**X**	
UNCOMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing, swelling of the face, lips, tongue or throat.			**X**
Angioedema (Serious swelling under the skin): swelling of the face, throat, arms, legs or genitals, rash or hives, pain and warmth of affected areas, throat tightness, difficulty breathing, trouble			**X**

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
swallowing, abdominal pain, vomiting, feeling dizzy, chest pain.			
Decreased levels of white blood cells: infections, fatigue, fever, aches, pains and flu-like symptoms.		**X**	
Hepatitis B virus reactivation: fever, tiredness, yellow skin or to the whites of eyes, abdominal pain, diarrhea.		**X**	
Nausea	**X**		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store TAVNEOS at room temperature (15°C - 30°C) and in the original package.

Keep out of reach and sight of children.

If you want more information about TAVNEOS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.otsukacanada.com), or by calling 1-877-341-9245.

This leaflet was prepared by Otsuka Canada Pharmaceutical Inc.

Last prepared APR 19, 2022