ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10 mg of avacopan.

Excipient with known effect

Each hard capsule contains 245 mg of macrogolglycerol hydroxystearate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Capsules with yellow body and light orange cap with “CCX168” in black ink.
One capsule has a length of 22 mm and a diameter of 8 mm (size 0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) (see section 4.2).

4.2 Posology and method of administration

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

Posology

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

Tavneos should be administered in combination with a rituximab or cyclophosphamide regimen as follows:
- 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 and 5.1.

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:
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is more than 3 times 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,
- ALT or AST > 5 × ULN for more than 2 weeks,
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalised 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.

Special populations

Elderly

No dose adjustment is required in elderly patients (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see section 5.2).

Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

Renal impairment

No dose adjustment is needed based on renal function (see section 5.2).

Avacopan 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 m², who are on dialysis, in need of dialysis or plasma exchange.

Severe disease manifested as alveolar haemorrhage

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

Paediatric population

The safety and efficacy of avacopan in adolescents (12 to 17 years of age) have not yet been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made. The safety and efficacy of avacopan in children below 12 years of age have not yet been established. No data are available.

Method of administration

This medicinal product 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 avacopan (see section 4.5).

4.3 Contraindications

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

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 avacopan in combination with cyclophosphamide (followed by azathioprine or mycophenolate) or rituximab, and trimethoprim and sulfamethoxazole. In the post-marketing setting, drug-induced liver injury and vanishing bile duct syndrome (VBDS), including cases with fatal outcome, have been reported (see section 4.8).

Avacopan must be avoided in patients with signs of liver disease, such as elevated AST, ALT, alkaline phosphatase (ALP), or total bilirubin > 3 times ULN.

Hepatic transaminases and total bilirubin must be obtained prior to initiation of therapy.

Patients must be monitored for hepatic transaminases and total bilirubin as clinically indicated and as part of the routine follow-up of patient's underlying condition (see section 4.2).

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).

Treatment with avacopan must not be initiated if WBC count is $< 3.5 \times 10^9$/L, or neutrophil count $< 1.5 \times 10^9$/L, or lymphocyte count $< 0.5 \times 10^9$/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 avacopan in combination with rituximab or cyclophosphamide (see section 4.8).

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 avacopan treatment, as appropriate according to local clinical practice guidelines.

Immunisation

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

Angioedema

Angioedema has been reported in patients receiving avacopan (see section 4.8).

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

Avacopan 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 avacopan is to be avoided (see section 4.5).
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 in case of any reoccurrence of disease activity.

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).

Macrogolglycerol hydroxystearate content

This medicinal product contains macrogolglycerol hydroxystearate, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Avacopan is a substrate of CYP3A4. Co-administration of inducers or inhibitors of this enzyme 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, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with avacopan is to be avoided (see section 4.4). 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 product with avacopan 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, 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. 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 other medicinal products

Avacopan is a weak 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, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus). Be cautious when these medicinal products are used with avacopan. Patients must be managed according to the summary of product characteristics of the respective medicinal products with a narrow therapeutic index.

Effect of macrogolglycerol hydroxystearate on sensitive P-glycoprotein (P-gp) substrates

A clinically relevant effect of the excipient macrogolglycerol hydroxystearate 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

Women of childbearing potential/Pregnancy

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

Studies in animals have shown reproductive toxicity (see section 5.3).

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

Breast-feeding

Avacopan has not been measured in milk of lactating animals; however, avacopan has been detected in the plasma of nursing animal offspring without apparent offspring effects (see section 5.3).

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 avacopan, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of avacopan on human fertility. Animal data did not indicate any impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 and in the post-marketing setting in patients treated with avacopan are listed in Table 1 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 1: 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, Rhinitis, Urinary tract infection, Sinusitis, Bronchitis, Gastroenteritis, Lower respiratory tract infection, Cellulitis, Herpes zoster, Influenza, Oral candidiasis, Oral herpes, Otitis media		
Blood and lymphatic system disorders		Neutropenia[1]		
Nervous system disorders	Headache			
Gastrointestinal disorders[1]	Nausea, Diarrhoea, Vomiting	Abdominal pain upper		
Hepatobiliary disorders	Liver function test increased[1,2]			Drug-induced liver injury[1], Vanishing bile duct syndrome[1]
Skin and subcutaneous tissue disorders			Angioedema[1]	
Investigations	White blood cell count decreased[3]	Blood creatine phosphokinase increased[1]		

1 See section "Description of selected adverse reactions".
2 Alanine aminotransferase increased, total blood bilirubin increased, hepatic function abnormal, gamma glutamyl transferase increased, hepatic enzyme increased, transaminases increased.
3 Includes leukopenia.

Description of selected adverse reactions

Hepatotoxicity

In the pivotal phase 3 study in which 330 patients were dosed, 13.3% of patients in the avacopan group and 11.6% of patients in the prednisone group had an adverse reaction of elevated liver function test (LFT).
In the avacopan group, LFT increased was reported in the phase 3 study and 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.

In the pivotal phase 3 study, 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 avacopan 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 avacopan 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.

Drug-induced liver injury and vanishing bile duct syndrome (VBDS) have been reported in the post-marketing setting (see section 4.4).

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 avacopan group.

The patient in the avacopan 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 avacopan 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 avacopan group had an adverse reaction of angioedema. One patient was hospitalised for the event. Avacopan was paused and both events resolved without sequelae. Avacopan 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%).

Special populations

Paediatric population

A total of 3 adolescents were studied in the phase 3 study, one in the prednisone group and two in the avacopan group. There are no data in children below 12 years of age (see section 5.1).

Elderly patients

The safety profile was similar between patients ≥ 65 years of age and adult patients < 65 years of age in the clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Avacopan 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.

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.

Pharmacodynamic effects

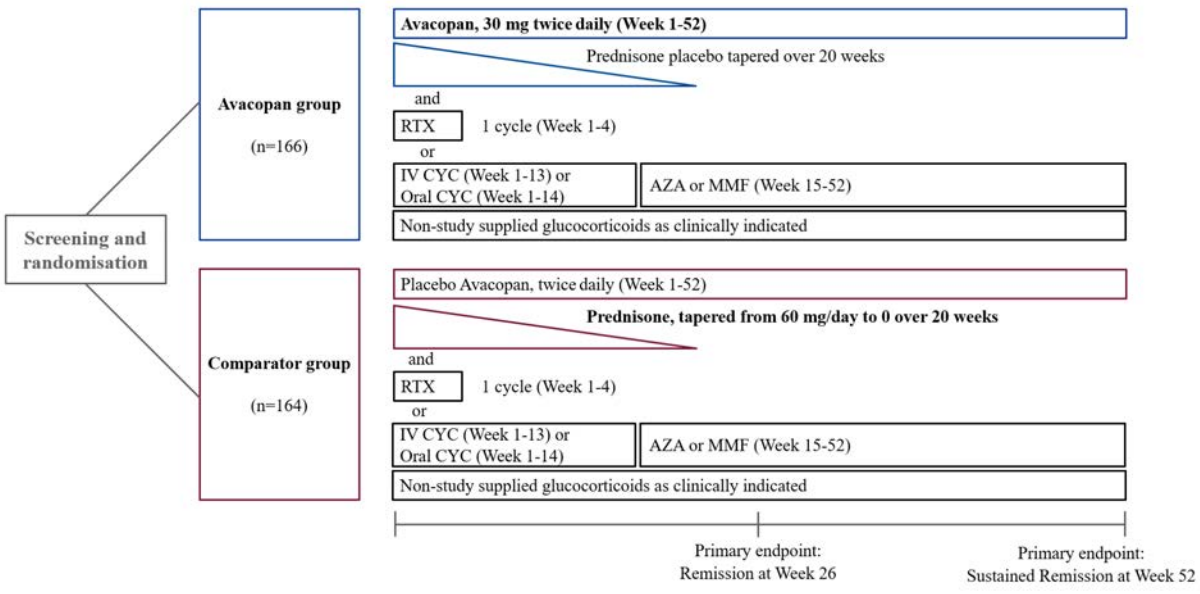
Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitis disease process.

Clinical efficacy and safety

A total of 330 patients aged 13 years or older 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 maximize safety of these medicinal products.

The following study-supplied glucocorticoid tapering schedule was used (Table 2).

Table 2: 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 3).

Table 3: 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 (%)		
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 in patients 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.

Results from this study are showed in Table 4.

Table 4: 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 (%)	Comparator N = 164 n (%)	Estimate of Treatment Difference in %[a]
Remission at week 26	120 (72.3)	115 (70.1)	3.4
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[b]
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.

[b] superiority p value = 0.013 (2-sided)

The efficacy observed was consistent across pertinent subgroups, i.e., those with newly-diagnosed and relapsed disease, PR3 and MPO ANCA positive, GPA and MPA, and men and women. Efficacy results by background treatment are presented in Table 5.

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

	Avacopan n/N (%)	Comparator n/N (%)	Difference in %, 95% CI[a]
Remission at week 26			
Patients receiving intravenous rituximab	83/107 (77.6)	81/107 (75.7)	1.9 (−9.5, 13.2)
Patients receiving intravenous or oral cyclophosphamide	37/59 (62.7)	34/57 (59.6)	3.1 (−14.7, 20.8)
Sustained remission at week 52			
Patients receiving intravenous rituximab	76/107 (71.0)	60/107 (56.1)	15.0 (2.2, 27.7)
Patients receiving intravenous or oral cyclophosphamide	33/59 (55.9)	30/57 (52.6)	3.3 (−14.8, 21.4)

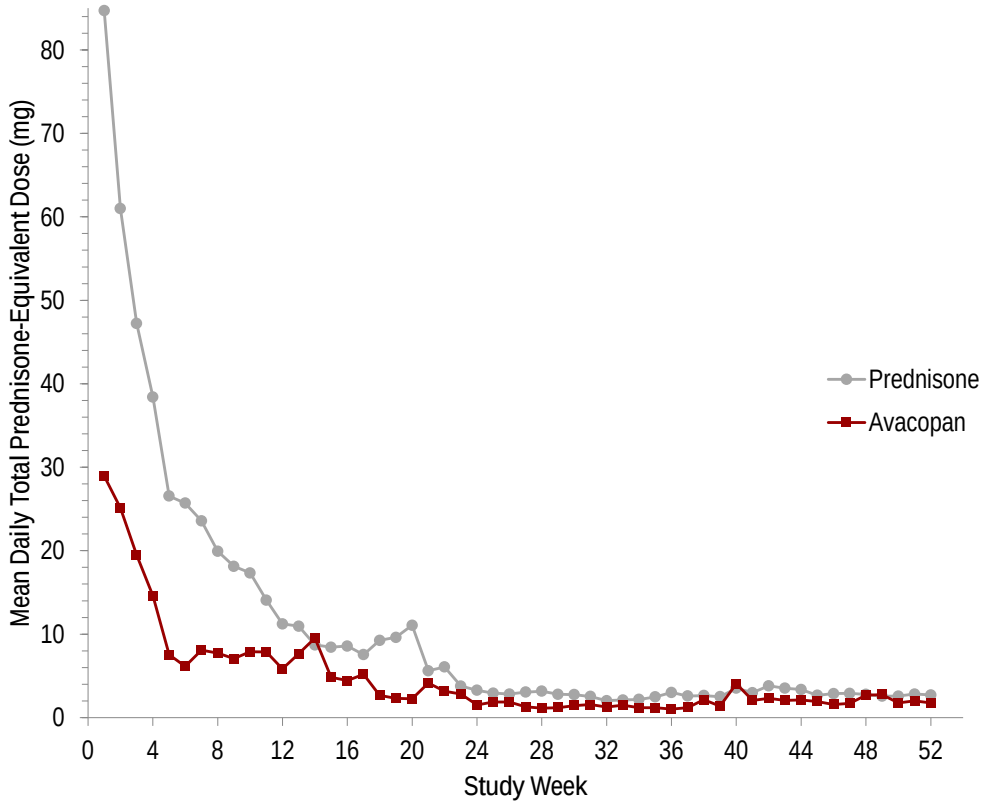
[a] Two-sided 95% confidence intervals (CI) are calculated for the difference in proportions (avacopan minus comparator) using the Wald method.

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).

From baseline to week 26, 86.1 % of patients using avacopan received non-study supplied glucocorticoids. In the comparator group, the majority of glucocorticoids use was due to the protocol-defined prednisone course.

Figure 2: Total mean daily prednisone-equivalent glucocorticoid dose per patient by study week in the ADVOCATE study (Intent-to-Treat Population)



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 summarised 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	**Comparator N = 164**	**Difference between Groups, 95% CI**
Cumulative Worsening Score (CWS)			
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 (AIS)			
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)

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with avacopan in one or more subsets of the paediatric population in treatment of ANCA-associated vasculitis (see section 4.2 for information on paediatric use).

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 reversible 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.

Biotransformation

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 metabolite M1.

Avacopan is a weak inhibitor of CYP3A4 and CYP2C9 as indicated by a modest increase in the AUC of the probe active substances midazolam (1.81-fold) and celecoxib (1.15-fold), respectively.

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.

Elimination

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.

Special populations

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).

Hepatic impairment

The pharmacokinetic 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 (mean ratios of C_{max} and AUC ≤ 1.3) of avacopan or its major metabolite M1 was observed; therefore, no dose adjustment is necessary (see section 4.2).

Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) (see section 4.2).

Renal impairment

Based on population pharmacokinetic analysis, the plasma exposure of avacopan is similar between patients with renal impairment and healthy subjects. Therefore, no dose adjustment is necessary based on renal function (see section 4.2).

Avacopan 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Fertility and early embryonic development

Avacopan produced no effects on male or female reproductive performance (fertility) or early development in hamsters at oral doses equivalent up to 6.8-fold the clinical AUC.

Embryo-foetal development

Avacopan was not teratogenic when dosed orally to hamsters and rabbits. In hamsters, an increased incidence of skeletal variations (short thoracolumbar supernumerary rib) was observed at exposure equivalent to 5.3-fold the clinical AUC. In rabbits, avacopan caused maternal toxicity (adverse clinical signs and abortions), but no foetal toxicity at 0.6-fold the clinical AUC.

Pre- and post-natal development

Avacopan did not result in adverse effects in female offspring when administered in hamsters at exposures up to 6.3-fold the clinical AUC during gestation and through lactation until weaning. In males, there was a slight delay in preputial separation at 3.7-fold the clinical AUC. This isolated finding was considered to be of low toxicological significance and was not associated with any impairment of reproductive performance.

Analysis of avacopan plasma levels in the lactating dams and the plasma levels in nursing offspring showed the presence of avacopan, suggesting that avacopan is likely secreted into the milk of lactating hamsters.

Carcinogenicity

The carcinogenic potential of avacopan was evaluated in a 2-year study in both rats and hamsters. In male rats, a slightly increased incidence of C-cell thyroid adenoma was noted in avacopan-treated rats; this increase was not statistically significant, and the incidence was within the historical control range. Avacopan was not carcinogenic in hamsters, the pharmacologically relevant species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Macrogolglycerol hydroxystearate
Macrogol (4000)

Capsule shell

Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Polysorbate 80

Imprinting ink

Black iron oxide (E172)
Shellac
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
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 or multipack of 540 hard capsules (3 packs of 180).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1605/001
EU/1/21/1605/002
EU/1/21/1605/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 30 AND 180 CAPSULES PACKS

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules
avacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg avacopan.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules.
30 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Capsules must be swallowed whole and taken with meal.
Do not crush, chew or open.
Read the package leaflet before use.

'QR code to be included' + www.tavneos-patient.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1605/001 – 30 hard capsules
EU/1/21/1605/002 – 180 hard capsules

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tavneos

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INNER PACKAGING

INNER CARTON PART OF A MULTIPACK (WITHOUT BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules
avacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg avacopan.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules.
Component of a multipack. Can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Capsules must be swallowed whole and taken with meal.
Do not crush, chew or open.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1605/003 – 540 hard capsules (3 packs of 180)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tavneos

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (MULTIPACK) - 540 (3 PACKS OF 180) HARD CAPSULES (WITH BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules
avacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg avacopan.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules.
Multipack: 540 (3 packs of 180) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Capsules must be swallowed whole and taken with meal.
Do not crush, chew or open.
Read the package leaflet before use.

'QR code to be included' + www.tavneos-patient.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1605/003 – 540 hard capsules (3 packs of 180)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tavneos

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules
avacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg avacopan.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate.

4. PHARMACEUTICAL FORM AND CONTENTS

180 hard capsules.
30 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Capsules must be swallowed whole and taken with meal.
Do not crush, chew or open.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect form light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1605/001 – 30 hard capsules
EU/1/21/1605/002 – 180 hard capsules
EU/1/21/1605/003 – 540 hard capsules (3 packs of 180)

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tavneos 10 mg hard capsules
avacopan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tavneos is and what it is used for

What is Tavneos?

Tavneos contains the active substance avacopan, which attaches to a specific protein in the body, called complement 5a receptor.

What is Tavneos used for?

Tavneos is used to treat adults with a gradually worsening disease caused by inflammation of the small blood vessels, called granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA):
- **Granulomatosis with polyangiitis** mainly affects small blood vessels and tissues in the kidneys, lung, throat, nose and sinuses, but also other organs. Patients develop small lumps (granulomas) in and around blood vessels, which are formed by tissue damage caused by inflammation.
- **Microscopic polyangiitis** affects the smaller blood vessels. It often affects the kidneys but may also affect other organs.

Complement 5a receptor has a key role in stimulating inflammation. This medicine attaches to it and prevents it from working, thereby reducing inflammation of blood vessels seen in these diseases.

Tavneos can be used together with other treatments prescribed by your doctor.

2. What you need to know before you take Tavneos

Do not take Tavneos

- if you are allergic to avacopan or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor before taking Tavneos and during treatment if you had or have:
- symptoms of a liver injury such as feeling sick (nausea or vomiting), feeling tired, loss of appetite, yellowing of the skin or eyes, dark urine, itching, upper stomach pain, increased levels of total bilirubin, the yellow breakdown substance of blood pigment, or of liver enzymes such as transaminases
- any infection, unexpected bruising and bleeding (these two are common signs of bone marrow failure)
- hepatitis B, hepatitis C, HIV infection or tuberculosis
- a heart disease, such as heart attack, heart failure, inflammation of heart blood vessels
- any type of cancer.

Tavneos is not recommended in patients with
- an active liver disease, or
- an active, serious infection.

Your doctor will carry out blood tests before and when necessary during treatment, to check:
- any problems with your liver (by measuring liver enzymes and total bilirubin in the blood)
- your risk of getting infections (by measuring the white blood cell count).

Your doctor will decide to temporally stop or permanently discontinue treatment.

Your doctor will also monitor you for signs and symptoms of an infection called *Neisseria meningitidis*. This is recommended for adult patients with GPA or MPA.

It is recommended that you have treatment to prevent the lung infection *Pneumocystis jirovecii* pneumonia during treatment with Tavneos.

It is recommended to give vaccinations before treatment with Tavneos or when there is no active disease (granulomatosis with polyangiitis or microscopic polyangiitis).

Severe and often painful swelling under the skin, mainly in the face, has been reported during treatment with Tavneos. If this affects the throat it can make it hard to breathe. Stop treatment and seek urgent medical advice if swelling of the face, lips, tongue or throat, or breathing difficulties occur.

Children and adolescents

Do not give this medicine to children under 18 years as there is not enough evidence to know if this medicine is safe and effective in this age group.

Other medicines and Tavneos

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is important to tell your doctor especially if you use any of the following medicines:
- carbamazepine, phenobarbital, phenytoin: medicines to treat epilepsy and other illnesses
- enzalutamide, mitotane: medicines to treat cancer
- rifampicin, a medicine to treat tuberculosis or certain other infections

- St. John’s wort, an herbal medicine used for mild depression.

If short-term use of one of these medicines cannot be avoided during treatment with Tavneos, your doctor may regularly check your condition to see how well Tavneos is working.

Tavneos can affect or be affected by the following medicines.
- alfentanil: a painkiller used during an operation with anaesthetics
- boceprevir, telaprevir: medicines to treat hepatitis C
- bosentan: a medicine to treat high blood pressure in the lungs, and sores on the fingers and toes called scleroderma
- clarithromycin, telithromycin: antibiotic medicines to treat bacterial infections
- conivaptan: a medicine to treat low blood sodium levels
- ciclosporin: a medicine to suppress the immune system and prevent transplant rejection, treat severe skin diseases and severe eye or joint inflammation
- dabigatran: a blood thinning medicine
- dihydroergotamine, ergotamine: medicines to treat migraine
- fentanyl: a strong painkiller
- indinavir, efavirenz, etravirine, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir: medicines to treat HIV infections
- itraconazole, posaconazole, voriconazole: medicines to treat fungal infections
- ketoconazole: a medicine to treat symptoms caused by the body’s excessive production of cortisol called Cushing’s syndrome
- mibefradil: a medicine to treat irregular heart rhythm and high blood pressure
- modafinil: a medicine to treat an extreme tendency to fall asleep
- nefazodone: medicines to treat depression
- sirolimus, tacrolimus: medicines to suppress the immune system and prevent transplant rejection.

Tavneos with food and drink

Avoid grapefruit and grapefruit juice during treatment with Tavneos, as these can influence the effect of the medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **Pregnancy**
  This medicine is not recommended during pregnancy or in women of childbearing potential not using contraception.
- **Breast-feeding**
  It is unknown whether avacopan passes into breast milk. A risk to the baby cannot be excluded. Your doctor will help you decide whether to stop treatment with Tavneos or stop breast-feeding.

Driving and using machines

It is considered unlikely that Tavneos will affect your ability to drive or to use machines.

Tavneos contains macrogolglycerol hydroxystearate

This may cause stomach upset and diarrhoea.

3. How to take Tavneos

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is **3 capsule**s **in the morning and 3 capsules in the evening.**

Method of administration

Swallow the capsules whole with one glass of water. **Do not** crush, chew or open the capsules. Take the capsules with a meal, 3 capsules in the morning and 3 capsules in the evening.

If you take more Tavneos than you should

Talk to your doctor immediately.

If you forget to take Tavneos

If you have **more than 3 hours to go** until your next scheduled dose, take the missed dose as soon as possible and then take your next dose at the right time.

If it is **less than 3 hours** to your next dose, do not take the missed dose. Just take your next dose at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Tavneos

Stop treatment and seek urgent medical advice if swelling of the face, lips, tongue or throat, or breathing difficulties occur. In any other situations, do not stop taking this medicine without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if the following serious side effects occur:
Very common (may affect more than 1 in 10 people)
- blood test showing increased levels of
  - liver enzymes (a sign of liver problems)
  - bilirubin: a yellow breakdown substance of the blood pigment.

Common (may affect up to 1 in 10 people)
- lung inflammation (symptoms can be wheezing, difficulty breathing, or chest pain).

Uncommon (may affect up to 1 in 100 people)
- serious allergic reaction which causes swelling under the skin, mainly in the face, and may cause breathing difficulties (angioedema).

Not known (frequency cannot be estimated from the available data)
- serious liver injury and bile duct injury (symptoms can be feeling sick (nausea or vomiting), feeling tired, loss of appetite, yellowing of the skin or eyes, dark urine, itching, or upper stomach pain). (See section 2.)

Other side effects can occur with the following frequencies:
Very common
- infection of the upper airways
- sore and inflamed throat and nose
- headache
- feeling sick (nausea)
- diarrhoea
- vomiting
- decreased white blood cell count seen in blood tests.

Common
- inflammation of the inner lining of the nose which causes sneezing, itching, runny and blocked nose
- urinary tract infections
- inflammation of the sinuses or bronchial tubes
- inflammation of the stomach and bowel lining
- infection of the lower airways
- cellulitis
- shingles
- flu
- Candida yeast fungal infection or herpes in the mouth
- middle ear infection
- reduced number of white blood cells called neutrophils (symptoms can be infections, fever or painful swallowing)
- upper abdominal pain
- increased blood level of creatine phosphokinase enzyme (symptoms can be chest pain, confusion, muscle ache and pain, sudden weakness or numbness of the body).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tavneos

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in the original bottle in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tavneos contains

- The active substance is avacopan.
  Each hard capsule contains 10 mg of avacopan.
- The other ingredients are:

– macrogolglycerol hydroxystearate
– macrogol (4000)
– gelatin
– polysorbate 80
– red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172)
– titanium dioxide (E171)
– shellac
– potassium hydroxide.

What Tavneos looks like and contents of the pack

Tavneos hard capsules are made of a yellow body and light orange cap with “CCX168” in black ink. Capsules are 22 mm long, with a diameter of 8 mm.
The capsules are packed in plastic bottles with a child-resistant closure.

Tavneos is available in
- packs containing 30 hard capsules or
- packs containing 180 hard capsules or
- multipacks containing 540 hard capsules (3 individual packs of 180 hard capsules).

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Vifor Fresenius Medical Care Renal Pharma France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris la Défense Cedex
France

Manufacturer

Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Detailed information on this medicine is also available on the following URL: http://www.tavneos-patient.eu.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for avacopan, the scientific conclusions of PRAC are as follows:

In view of available data on drug-induced liver injury (DILI) and vanishing bile duct syndrome (VBDS) from spontaneous reports and the literature, including 8 cases of DILI with a compatible time to onset (TTO)(<90days) and a positive dechallenge, at least 12 serious cases of liver enzyme elevations suggestive of DILI grade 3 or 4 with a compatible TTO and 3 cases of VBDS, confirmed by biopsy with a compatible TTO (<60 days), the PRAC considers a causal relationship between avacopan and DILI and between avacopan and VBDS is at least a reasonable possibility. The PRAC concluded that the product information of products containing avacopan as per EURD list should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisations

On the basis of the scientific conclusions for avacopan the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing avacopan is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisations should be varied.