Primary Immunodeficiencies / Autoinflammatory Disorders
Autoimmune Diseases / Paediatric Rheumatic Diseases

Guidelines for the use of plasma exchange, corticosteroids and complement inhibitors in the management of ANCA-Associated Vasculitis in Ireland

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Introduction

Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Eosinophilic granulomatosis with polyangiitis (EGPA) are together termed the ANCA-associated vasculitides (AAV)[1]. These are rare autoimmune multi-system disorders with an annual incidence of 15/million and prevalence of approximately 1/5,000.

AAV are chronic relapsing conditions that require coordinated long term multi-disciplinary input. The goal of these guidelines is to assist Irish clinicians to standardise and harmonise their approach to the management of AAV, accounting for recent advances in complement inhibitor therapeutics and plasma exchange. Thus, every person with AAV in Ireland should have access to the same high standard of care, with effective use of high cost immunotherapy in line with international best practice.

In 2009, 2016 and 2022 the European League Against Rheumatism (EULAR) have published extensive peer reviewed recommendations for managing primary systemic vasculitis which included the management of AAV. The most recent EULAR Guideline outlines a standardised approach to the treatment of AAV, including 4 over-arching principles and 17 recommendations[2]. RITA-Ireland recommends the adoption of the EULAR Guideline in full.

We further expand on this to provide guidance regarding the role of the novel complement inhibitor Avacopan in AAV, considerations on the use of plasma exchange and steroid dosing protocols.

Diagnosis of AAV

A diagnosis of AAV typically requires:

1. A compatible clinical syndrome (which may include, but is not limited to, any or all of the following: polyarthritis, vasculitic skin rash, glomerulonephritis, scleritis / conjunctivitis, focal neurological signs, sinusitis, deafness, nasal cartilage destruction, lung nodules, pulmonary haemorrhage, GI bleeding/perforation)

2. Positive ANCA testing by ELISA (for anti-PR3 or anti-MPO antibodies) AND/OR

3. Consistent histological findings (which may include pauci-immune focal necrotising glomerulonephritis, granulomatous inflammation in lung or nasal tissue, or necrotising vasculitis in any samples tissue). Histological confirmation is strongly recommended in all cases of suspected AAV while recognising that in a small number of cases this may not be possible due to clinical factors. Initiation of therapy in organ or life-threatening disease should not be delayed while awaiting histological confirmation.

4. The absence of a secondary cause of vasculitis (e.g. endocarditis).

In practice, it may not be possible to confirm all 4 diagnostic components prior to initiation of therapy.

Stratification of Disease Severity

Patients with AAV have previously been sub-categorised into those with ‘severe’ and ‘non-severe’ disease. However, the terms ‘severe/non-severe’, ‘limited’ or ‘early-systemic’ are open to interpretation and risk the under treatment of patients at risk of life- or organ-threatening disease.

We concur with the EULAR Guideline from 2016 and 2022 that patients be categorised in two groups; those with and those without organ-threatening or life-threatening disease[2].

Disease Activity Status in AAV:

Active	Presence of typical signs, symptoms or other features (such as glomerulonephritis or pulmonary nodules) of active AAV. In practice, a Birmingham Vasculitis Activity Score (BVAS) >/=1. This generally leads to a clinical decision to escalate treatment.
Remission	Absence of typical signs, symptoms, or other features of active AAV with or without immunosuppressive therapy
Sustained Remission	Absence of typical signs, symptoms, or other features of active AAV over a defined time period with or without immunosuppressive therapy
Response	≥50% reduction of disease activity score (BVAS) and absence of new manifestations
Relapse	Recurrence of AAV after a period of remission
Refractory	Unchanged or increased signs, symptoms or other features of active AAV after a period of standard induction therapy. Damage, infections, side effects of treatment or comorbidities as potential causes of the persistent or worsened disease manifestations need to be ruled out.

Therapy for Patients with AAV

In line with the 2022 EULAR Guidelines the following approach is recommended for patients presenting with a diagnosis of *de novo* or relapsing AAV. It is important that patients with AAV are managed in close collaboration with, or at, centres of expertise. In the Irish context this includes, but is not limited to, RITA-Ireland centres. Patients should expect their treating centre to afford rapid access to specialists with expertise in AAV, immunological monitoring, the use of rituximab in patients with inflammatory disease, specialised radiography, diagnostic histopathology, assessment of eye / ENT involvement and plasma exchange, as defined in the HSE-approved care pathway.

Avacopan

This Guideline acknowledges the EULAR and CanVasc recommendations on the use of Avacopan as an adjunct to induction therapy with corticosteroids (CS) and rituximab and / or cyclophosphamide in MPA and GPA[2,6].

Avacopan has been available for use in Ireland since July 1, 2024, in combination with rituximab and/or cyclophosphamide, for the treatment of adult patients with GPA or MPA and evidence of 'severe', active vasculitis. In practice the term 'severe' reflects the inclusion criteria for the ADVOCATE Trial[3]: eGFR of at least 15 ml/minute/1.73 m^2 of body-surface area; **at least one major or three nonmajor items** or at least **two renal items of hematuria and proteinuria** on the Birmingham Vasculitis Activity Score (BVAS). Avacopan may reduce harms associated with corticosteroid (CS) therapy in AAV; however, it has not been studied in patients with EGPA or pulmonary haemorrhage, nor in those with an eGFR <15 mL/min/1.73 m^2, who are on dialysis or receiving plasma exchange.

Background:

Avacopan is a selective antagonist of the human complement 5a receptor 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.

EMA approval for the use of Avacopan in AAV is based on the result of the Phase III, placebo-controlled ADVOCATE trial (Avacopan spc, Appendix 1). This trial randomised 330 patients with newly diagnosed or relapsing GPA or MPA treated with either rituximab or cyclophosphamide (followed by azathioprine) to receive either Avacopan 30 mg twice daily for 52 weeks, or CS on a tapering schedule for 20 weeks similar to the RAVE study. Intravenous pulse CS were allowed up to a maximum of 3g before and during trial enrolment. Non-study-provided CS were allowed in both groups during the screening period, but had to be tapered to 20 mg or less prednisone-equivalent before entry into the trial, and had to be discontinued by the end of week 4 in the avacopan group. Intravenous pulse CS were allowed in cases of worsening or relapsing disease. It is important to note that patients in both study arms received open-label CS for a variety of reasons. The mean total prednisone-equivalent doses of oral and intravenous glucocorticoids for the avacopan and prednisone groups were 1676 mg (equating to 5 mg per patient per day) in the avacopan group and 3847 mg (equating to 13 mg per patient per day) in the prednisone group a 56% reduction in total CS exposure. There was a greater incidence of CS-associated harmful effects in the control group compared to the avacopan group. The incidence of other major adverse events was not different between the control and avacopan arms.

Remission (BVAS of 0 plus no CS use in the previous 4 weeks) at 6 months was observed in 72.3% and 70.1% of patients in the avacopan and prednisone arms (non-inferior). Sustained remission at week 52 was observed in 65.7% and 54.9% of patients in the avacopan and prednisone arms, respectively, achieving superiority. In a post-hoc analysis, avacopan led to an earlier reduction in albuminuria, and an improvement in kidney function, especially in patients with eGFR <30 ml/min/1.73 m^2 and those with an eGFR <60 ml/min/1.73 m^2 plus urinary abnormalities at baseline suggesting a particular benefit in patients with renal involvement.

These results give confidence that avacopan is safe, demonstrates significant steroid-sparing capacity, with a higher remission rates at 12 months, when used in combination with rituximab or cyclophosphamide induction therapy. Avacopan also appears to improve early renal outcomes compared with a standard prednisone-based regimen.

Recommendation

- Avacopan should be considered as part of the induction regimen of patients with newly diagnosed or relapsing life- or organ threatening GPA or MPA.

- The cost of avacopan is substantial, significantly exceeding the costs for administering rituximab or mycophenolate mofetil. It is currently available on a restricted basis via the High Tech Hub. Patients at increased risk of CS toxicity (e.g. *obesity, osteoporosis, cardiovascular disease, psychiatric illness, susceptibility to recurrent or severe infections*) may benefit from avacopan as a strategy to limit CS exposure. Patients with renal involvement may also potentially benefit from a more rapid response to treatment using avacopan.

- The role of avacopan as an agent to treat refractory disease is an area of research. The use of avacopan should be accompanied by an early strategy to discontinue CS use, preferably to zero by 4 weeks. Avacopan should not be continued after 12 months without formal multidisciplinary discussion.

- Of note, avacopan should be used with caution in patients with eGFR <15 ml/min/1.73 m^2 or those with alveolar haemorrhage requiring mechanical ventilation, as these patients were excluded from the ADVOCATE Study.

- It is strongly encouraged that all patients receiving avacopan be enrolled in the RITA Ireland Vasculitis Registry (https://tinyurl.com/mpsetn6t) to facilitate audit of outcomes.

Plasma Exchange in AAV

Plasma exchange has been used for several decades to treat patients with AAV based on a plausible biological rationale (removal of circulating ANCA and /or other pro-inflammatory mediators) and a small number of clinical trials of modest size[1]. The PEXIVAS Trial published in 2020 was a large (n =704) randomised trial with a 2-by-2 factorial design to evaluate the use of plasma exchange and two regimens of oral CS in patients with severe ANCA-associated vasculitis (defined by an estimated glomerular filtration rate of <50 ml per minute per 1.73 m^2 or diffuse pulmonary hemorrhage)[4]. PEXIVAS failed to show a difference between PLEX and control for both the primary composite outcome of ESKD or all-cause mortality and for each of the components of the primary outcome separately. However, a subsequent meta-analysis has suggested that patients treated with plasma exchange have benefit from significant risk reduction in end stage kidney disease (ESKD), but not all cause mortality, at 12 months with uncertain effects on ESKD at later time points[5]. The reduction in the risk of ESKD at 12 months is paralleled by a relative increase in the risk of serious infection in the first year that may account for the absence of a mortality benefit in those treated with plasma exchange. Importantly, the benefits and risks of plasma exchange likely depend on the baseline risk of outcome. A higher estimated risk of ESKD prior to treatment initiation will associate with a larger relative risk reduction of ESKD due to plasma exchange at ESKD at one year. However, a high baseline risk of infection will also associate with a higher risk of serious infection with an associated but as yet undefined increase in mortality.

Therefore, the consideration of plasma exchange in MPA and GPA should balance the reported benefit in a subgroup of patients at high risk of ESKD (creatinine >300umol/l) against the risk of severe infection after discussion of the risks and benefits with the patient[7].

Corticosteroid Administration in AAV

For organ and/or life-threatening acute disease, up to 3 pulses of 0.25-0.5g methylprednisolone may be considered. High dose intravenous methylprednisolone should not be routinely administered to all patients with a new diagnosis of ANCA-associated vasculitis.

The PEXIVAS 'low dose' steroid protocol is preferred for remission induction (Table 1). It is considered useful to give patients an explicit written dosing schedule for their prednisolone taper and written explicit instructions not to stop their CS without consulting their treating physician. As outlined above

CS therapy should be withdrawn as soon as possible in patients receiving avacopan, assuming that an appropriate therapeutic response has been achieved.

Week	Low-dose PEXIVAS (mg)		
	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-26	5	5	5
26-	Local Practice		

Table 1: CS dosing schedule in accordance with PEXIVAS trial.

Patient Information

All patients with AAV should be given a clear verbal explanation of the nature of their disease and proposed treatment plan. This should be supplemented by written information. We recognise that the internet can provide immediate, easy access to reliable and up-to-date information and advice, and to patient support groups which provide the reassurance of peer support and the ability to share knowledge and experience. However, patients should be counselled that the internet can also provide incorrect, unproven and even dangerous information. A patient who understands and is educated about the disease is frequently better able to recognise the early signs and symptoms of relapse. ERN-RITA has developed patient journey information resources (https://ern-rita.org/patient-journeys/).

References

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5. Walsh M, Collister D, Zeng L, et. al.: The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ 2022; 376

6. Turgeon et al. CanVasc consensus recommendations for the use of avacopan in antineutrophil cytoplasm antibody-associated vasculitis: 2022 addendum. Rheumatology 2023 62(8):2646-2651

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Appendix 1. Tavneos SPC

Tavneos 10 mg hard capsules

Active Ingredient:
avacopan

Company:
Vifor Fresenius Medical Care Renal Pharma UK Ltd See contact details

ATC code:
L04AJ05

Healthcare Professionals (SmPC) Patient Leaflet (PIL)

Last updated on emc: 28 Aug 2024

Quick Links
Undesirable Effects Pharmacological Properties Interactions Posology Contraindications Excipients Storage precautions

Print SmPC information

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).

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 m^2, 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

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

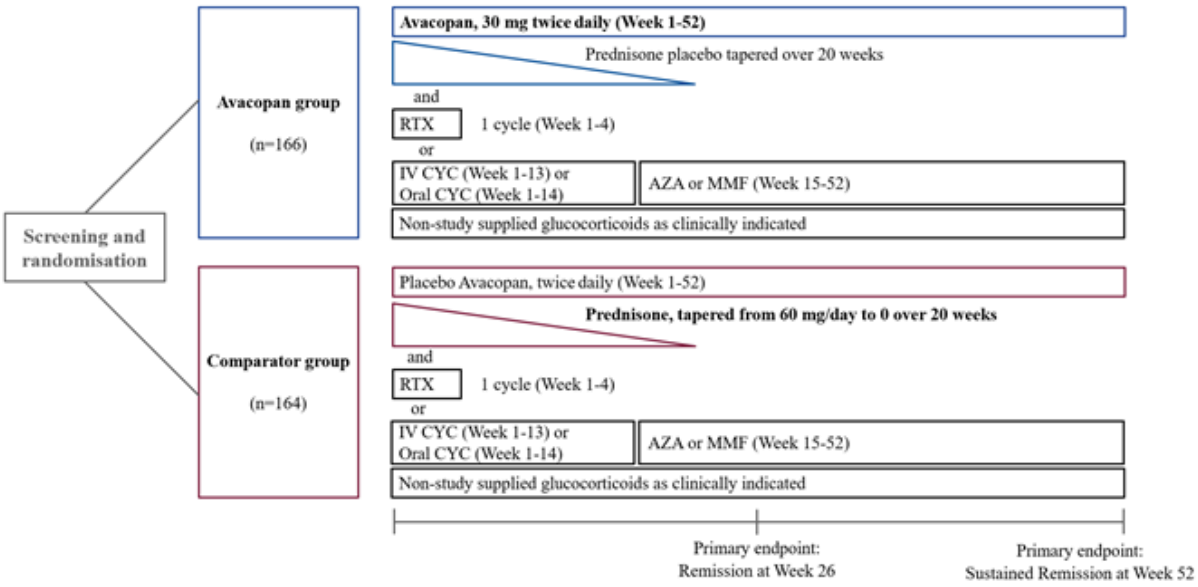
Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitis disease process.

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/m^2 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)

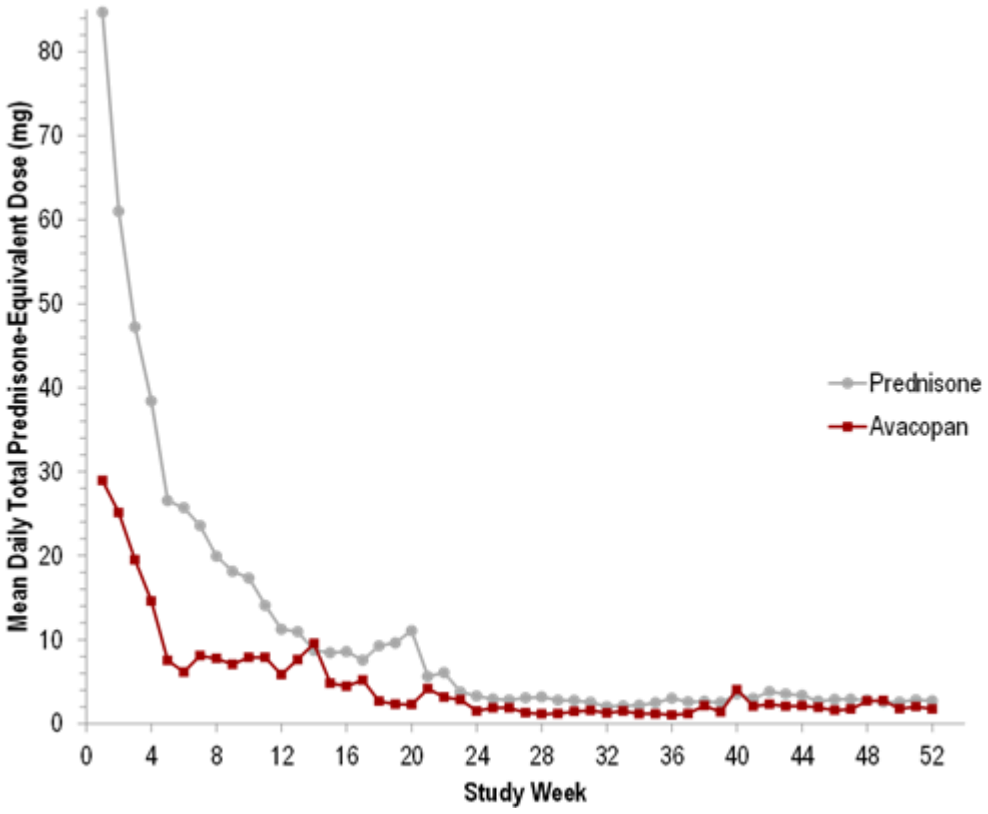
[a] Two-sided 95% confidence intervals (CI) are calculated for the difference in proportions (avacopan minus comparator) using the Wald method.

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 α 1-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 m^2, 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

4 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 Dé fense 8

92042 Paris la Dé fense Cedex

France

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

06/05/2022

10. Date of revision of the text

19/08/2024