11 January 2022
EMADOC-1700519818-748110
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Tavneos ((2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide)

Sponsor: Vifor Fresenius Medical Care Renal Pharma France

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Introductory comment

The approved therapeutic indication "Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) and or microscopic polyangiitis (MPA)", falls within the scope of the three designated orphan conditions "treatment of microscopic polyangiitis", and "treatment of granulomatosis with polyangiitis'' and are covered in this one document.

1. Product and administrative information

Orphan medicinal product designation procedural history

EU/3/14/1372

Product	
Designated active substance	(2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide
Other name	Avacopan
International Non-Proprietary Name	Avacopan
Tradename	Tavneos
Orphan condition	Treatment of microscopic polyangiitis
Sponsor's details:	Vifor Fresenius Medical Care Renal Pharma France Tour Franklin La Defense 8 101 Terrasse Boieldieu Paris La Defense Cedex 92042 France
Orphan medicinal product designation procedural history	
Sponsor/applicant	ChemoCentryx Limited
COMP opinion	09 October 2014
EC decision	19 November 2014
EC registration number	EU/3/14/1372
Post-designation procedural history	
Transfer of sponsorship	Transfer from ChemoCentryx Limited to Chemocentryx Ireland Limited– EC decision of 21 February 2019 Transfer from Chemocentryx Ireland Limited to Vifor Fresenius Medical Care Renal Pharma France – EC decision of 09 October 2020

EU/3/14/1373

Product	
Designated active substance	(2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide
Other name	Avacopan
International Non-Proprietary Name	Avacopan
Tradename	Tavneos
Orphan condition	Treatment of granulomatosis with polyangiitis

Sponsor's details:	Vifor Fresenius Medical Care Renal Pharma France Tour Franklin La Defense 8 101 Terrasse Boieldieu Paris La Defense Cedex 92042 France
Orphan medicinal product designation procedural history	
Sponsor/applicant	ChemoCentryx Limited
COMP opinion	09 October 2014
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Post-designation procedural history	
Transfer of sponsorship	Transfer from ChemoCentryx Limited to Chemocentryx Ireland Limited– EC decision of 21 February 2019 Transfer from Chemocentryx Ireland Limited to Vifor Fresenius Medical Care Renal Pharma France – EC decision of 09 October 2020

Marketing authorisation procedural history

Rapporteur / Co-rapporteur	Kristina Dunder / Outi Mäki-Ikola
Applicant	Vifor Fresenius Medical Care Renal Pharma France
Application submission	09 October 2020
Procedure start	29 October 2020
Procedure number	EMA/H/C/005523/0000
Invented name	Tavneos
Proposed therapeutic indication	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) Further information on Tavneos can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/tavneos
CHMP opinion	11 November 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Elisabeth Johanne Rook / Darius Matusevicius
Sponsor's report submission	21 May 2021
COMP discussion	03-05 November 2021
COMP opinion (adoption via written procedure)	12 November 2021

2. Grounds for the COMP opinions

EU/3/14/1372

The COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide was considered justified based on preclinical data in a relevant model of the disease and preliminary clinical data in patients with the condition indicating improvement in renal disease;
- the condition is chronically debilitating due to the progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure, as well as infections and malignancies as a consequence of available treatments;
- the condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.

EU/3/14/1373

The COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide was considered justified based on preliminary clinical data in patients with the condition indicating improvement in renal disease and reduced overall vasculitis activity;
- the condition is chronically debilitating due to progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure, as well as infections and malignancies as a consequence of available treatments;
- the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

- Microscopic polyangiitis (MPA)

Microscopic polyangiitis (MPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis that affects small to medium vessels (2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, Jenette et al, 2013). MPA may affect any organ, with a predilection for

the kidneys. MPA can be distinguished from other forms of small vessel vasculitides by the absence of granuloma formation, and the predominance of perinuclear ANCA staining by immunofluorescence and positive testing, predominantly for the myeloperoxidase (MPO) antigen. In contrast to other ANCA-associated vasulites, in particular granulomatosis with polyangiitis, MPA spares the upper respiratory tract.

MPA is an auto-immune disease with unknown aetiology. Environmental factors, such as Staphylococcus infections or exposure to silica dust, as well as genetic susceptibility have been discussed with HLA-DQ being a candidate gene among MPA patients. The peak age of onset is 65 to 74 years, men are slightly more often affected than women (1.5 : 1.0). Signs and symptoms comprise renal disease (haematuria and urinary RBC casts, albuminuria, decreased eGFR, hypertension, and sometimes as acute renal failure), pulmonary disease (infiltrates, cavitary lesions, pulmonary haemorrhage, and rarely bronchial stenosis), gastro-intestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea, and bloody stools), episcleritis, constitutional symptoms, fever, arthralgias, purpura, and neurologic disease (peripheral neuropathy, cerebral vasculitis). Renal disease occurs in around 80% of patients.

Diagnosis is based on presenting signs and symptoms, serology (positive cANCA antibody titers: anti-MPO antibodies in up to 75% of patients), chest X rays, and often renal biopsy (pauci-immune necrotizing crescentic glomerulonephritis). Disease activity is monitored using the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index (Mukhtyar et al, 2009; Exley et al, 1998; Luqmani et al, 1994).

- Granulomatosis with polyangitis (GPA)

Granulomatosis with polyangitis (GPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis that affects small to medium vessels (2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, Jenette et al, 2013). Classically, GPA is characterised by granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis, and nephritis (known as 'Wegener's triad', as the condition was previously named Wegener's granulomatosis). GPA may affect any organ, with a predilection for the upper and lower respiratory tracts and the kidneys.

GPA is an auto-immune disease with unknown aetiology. Environmental factors, such as Staphylococcus infections or exposure to silica dust, as well as genetic susceptibility have been discussed with HLA DPB1*0401 being candidate gene among European GPA patients. The peak age of onset is 65 to 74 years, men are slightly more often affected than women (1.5 : 1.0). Signs and symptoms comprise renal disease (hematuria and urinary RBC casts, albuminuria, decreased eGFR, hypertension and sometimes as acute renal failure), pulmonary disease (pulmonary nodules, so called 'coin lesions', infiltrates, cavitary lesions, pulmonary haemorrhage, and rarely bronchial stenosis), ear/nose/throat involvement (pain, stuffed nose, nosebleeds, crusting, saddle-nose deformity, hearing loss due to auditory tube dysfunction, sensoneural hearing loss, strawberry gingivitis, non-specific ulcerations of the oral mucosa, subglottal stenosis), constitutional symptoms, fever, arthralgias, purpura and neurologic disease. Upper and lower airway disease is the most common presenting feature of GPA, occurring in 70% to 90% of patients, renal disease is present in approximately 80% of patients.

The approved therapeutic indication "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)'' falls within the scope of the two designated

orphan conditions "Treatment of granulomatosis with polyangiitis" and "Treatment of microscopic polyangiitis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP on the basis of the submitted evidence including data from the randomised, double-blind, multicentre, pivotal phase 3 ADVOCATE study. For a full discussion of the results, please refer to the European Public Assessment Report of Tavneos.

Chronically debilitating and/or life-threatening nature

No change in the chronically debilitating and/or life-threatening nature of the conditions have been reported since the designation of the orphan medicinal product.

The condition is chronically debilitating due to progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure, as well as infections and malignancies, also as a consequence of available treatments. Patients with MPA have a 1-year mortality rate up to 23% (corral-Gudino et al, 2011). Patients with GPA have a 9-fold increased mortality risk in the first year of disease, compared to healthy controls. Main causes of death are infections, pulmonary complications, and renal disease. Cardiovascular disease is also common. Other adverse effects of long-term glucocorticoid therapy are osteoporosis, diabetes, hypertension, and ocular cataract. Cyclophosphamides increase the risk for bladder cancer, acute myeloid leukaemia, and non-melanoma skin cancer, and impact fertility. Around 40% of all patients develop end-stage renal disease requiring renal replacement therapy within 2 years after diagnosis (Jayne et al 2000).

Number of people affected or at risk

- Microscopic polyangiitis (MPA)

A PubMed literature search was conducted on 5-May-2021 with the following search terms to identify any new reports since the time of the application: "microscopic polyangiitis" OR "Wegener's" OR "granulomatosis with polyangiitis" OR "ANCA-associated vasculitis". Since the orphan drug application, no further relevant MPA publications were found.

A prevalence of AAV of 69.3 per million was reported in Turkey for the period of 2004 to 2014;60% of these were GPA (41.6 per million),30% MPA (20.8 per million), and 10% eosinophilic granulomatosis with polyangiitis (EGPA; 6.9 per million; Pamuk et al, 2016). The incidence of AAV in this study was 8.1 per million person-years; 4.8 for GPA, 2.4 for MPA, and 0.8 for EGPA. A study from Spain reported an annual incidence of AAV of 29 per million patient-years from 1994 through 2010; 10 for GPA, 16 for MPA, and 3 for EGPA (Romero-Gomez et al, 2015). This study also reported a prevalence of AAV of 44.8 per million; 15.8 for GPA, 23.8 for MPA, and 5.3 for EGPA. Hoang et al reported the frequency of various types of vasculitis as summarised in Table 1 (Hoang 2020).

Table 1. Incidence - Microscopic polyangiitis

Incidence per million	Location	Years of study (Reference)
8.0	Norwich, UK	1988–1997
2.7	Tromso, Norway	1988–1998
1.6	Olmsted County, Minnesota, USA	1996–2015
94	Southern Sweden	2003

The sponsor concludes on a prevalence of the condition of 0.94 per 10,000 in the EU, which was accepted by the COMP as a conservative estimate. However, the COMP considered that the prevalence should be reported as ''not more than 1 in 10,000''.

- Granulomatosis with polyangitis (GPA)

The sponsor has searched the PubMed database with the following search terms to identify any new reports since the time of the initial orphan application: "microscopic polyangiitis" OR "Wegener's" OR" granulomatosis with polyangiitis" OR "ANCA-associated vasculitis". A study from Poland (Kanecki et al 2018) used data from the Polish hospital morbidity study carried out by the National Institute of Public Health. This study examining the period 2011-2015 consisted of 1491 patients and estimated annual incidence at 7.7 per million population and prevalence at 0.36 per 10,000. This prevalence estimate was within the range found in the original orphan application in 2014 (0.24 to 1.57 per 10,000). Therefore, GPA remains an orphan disease with a prevalence ≤5 per 10,000 people.

Hoang et al reported the frequency of various types of vasculitis as summarised in Table 2 (Hoang 2020).

Table 2. Incidence - Granulomatosis with polyangiitis (Wegener granulomatosis)

Incidence per million	Location	Years of study (Reference)
10.6	Norwich, UK	1988–1997
63	United Kingdom	1988–1997
12.0	Tromso, Norway	1994–1998
95	Northern Norway	1988–1997
58	Northern Germany	1994
42	Southern Germany	1994
160	Southern Sweden	2003
1.3	Olmsted County, Minnesota, USA	1996–2015
23.7	US	

The COMP agrees that the prevalence has not been changed since the orphan designation of the product in 2014 and remains 1.6 per 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Treatment consists of two stages: an intensive induction treatment at the time of disease flare, followed by chronic maintenance therapy with milder immunosuppressive treatment regimens to prevent relapses and organ damage by chronic vasculitis.

Rituximab (in combination with corticosteroids) is the only approved treatment for the condition by a centralised procedure in the EU. It was approved in 2013 for the induction treatment of patients with GPA and MPA, and since 2017, also for the maintenance of GPA and MPA. Cyclophosphamide is also authorised in several member states for the treatment of Wegener's Disease, which is the same as GPA. Because of its toxicity, it is used as induction therapy of acute flares, usually followed by

azathioprine maintenance therapy according to treatment guidelines recommendations (e.g. EULAR/ERA-EDTA 2016)

The sponsor also states that in spite of not being authorised, corticosteroids, in combination according to the different phase of the condition are the mainstay treatments of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Methotrexate has been acknowledged as an alternative to cyclophosphamide in the induction phase for those patients with milder disease and normal renal function.

In addition to the above mycophenolate mofetil (MMF) is used in the treatment of the condition. Plasmapheresis has also been used in adult patients with severe progressive renal failure.

Significant benefit

The sponsor argues a clinically relevant advantage based on the outcome of the pivotal Phase 3 study (ADVOCATE) in patients with ANCA-associated vasculitis, which showed that avacopan is an effective treatment in these patients. A total of 330 patients aged 13 years or older with GPA (54.8%) or MPA (45.2%) were treated in the active-comparator, randomised, double-blind, double-dummy, multicentre, pivotal phase 3 ADVOCATE study for 52 weeks.

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)

Patients were stratified in two strata with different background treatments: rituximab IV induction (4W) therapy, followed by placebo between Week 13-52, or cyclophosphamide (12 W induction), followed by azathioprine (AZA) or MMF maintenance W13-52). About 70% of the study population received rituximab in the induction phase, as at the time of recruitment, Mabthera (rituximab) was not yet approved for maintenance therapy in GPA/MPA.

The following arguments are considered supportive for the significant benefit:

1. Superior efficacy in sustained remission at Week 52, and a lower relapse rate in the avacopan group compared to prednisone:

- Sustained remission at Week 52 was achieved in 90 of 164 subjects (54.9%) in the prednisone control group and 109 of 166 subjects (65.7%) in the avacopan group (P=0.0066 for superiority).
- A higher incidence of sustained remission at week 52 in the avacopan group compared to the prednisone group in the rituximab stratum, where subjects did not receive any protocol specified immunosuppressive treatment during the last 26 weeks. In the rituximab stratum, sustained remission at week 52 was achieved in 60 of 107 subjects (56.1%) in the prednisone group compared to 76 of 107 subjects (71.0%) in the avacopan group (P=0.0040 f or superiority).
- Avacopan was non-inferior to prednisone in achieving remission at week 26 on top of rituximab induction therapy or cyclophosphamide: Remission at week 26 was achieved in 115 of 164 subjects (70.1%) in the prednisone control group and 120 of 166 subjects (72.3%) in the avacopan group (P < 0.0001 for non-inferiority).

- The reduction in the incidence of relapse at any time after achievement of Birmingham vasculitis activity score (BVAS)=0 was statistically significant in the avacopan group compared to the prednisone group.

2. The medical outcomes survey short form-36 version 2 (SF-36v2) total score numerically improved more in the avacopan group than in the comparator group during the pivotal phase 3 study.

3. Renal function, a clinically relevant outcome was improved more in the avacopan group compared to the prednisone group. At week 52, the least squares mean (LSM) increase from baseline in Estimated glomerular filtration rate (Egfr) was 7.3 mL/min/1.73 m² in the avacopan group (from a baseline of 44.6 mL/min/1.73 m²) and 4.1 mL/min/1.73 m² in the comparator group (from a baseline of 45.6 mL/min/1.73 m²) (LSM difference 3.2, [95% CI 0.3, 6.1]).

4. Glucocorticoid toxicity was significantly reduced in the avacopan group compared to the prednisone group. The glucocorticoid toxicity index cumulative worsening score and the aggregate improvement score at weeks 13 and 26 were clinically and statistically lower in the avacopan group compared to the prednisone group, particularly regarding body mass index, glucose tolerance, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection components.

The significant benefit is also considered as demonstrated based on glucocorticoid saving properties of avacopan treatment on top of induction treatment. In addition, a benefit in renal outcomes was shown at longer term treatment as compared to standard of care azathioprine.

The COMP assessed the results from the pivotal trial for the total study population (combined for GPA and MPA patients). No subgroup analyses for the separate conditions were taken into consideration, as the study population was not stratified a priori based on their diagnosis MPA/GPA, and the study was neither powered to demonstrate an effect for each condition separately, which would be challenging given the rarity of the conditions. Subgroup analyses would also be challenging given the complex study design with multiple treatment strata.

Based on the above and taking into account the therapeutic indication which is covered by both orphan designated conditions "treatment of granulomatosis with polyangiitis" and ''treatment of microscopic polyangiitis'', the COMP considered that avacopan in combination with either rituximab or cyclophosphamide regimen was effective on top of standard of care in improving relevant clinical outcomes of MPA (and GPA), including parameters of renal function and overall vasculitis scores. The COMP concluded that the sponsor has provided sufficient arguments to justify that the product could be of significant benefit to patients affected by the condition(s).

4. COMP positions adopted on 12 November 2021

EU/3/14/1372

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of microscopic polyangiitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be not more than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to the progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal failure;

- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Tavneos may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data from the pivotal clinical trial demonstrating that Tavneos was effective on top of standard of care in improving relevant clinical outcomes of microscopic polyangiitis, including parameters of renal function and a relevant reduction of glucocorticoid treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tavneos, (2R,3S)-2-(4-cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide, avacopan for treatment of microscopic polyangiitis (EU/3/14/1372) is not removed from the Community Register of Orphan Medicinal Products.

EU/3/14/1373

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of granulomatosis with polyangiitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to progressive affection of the respiratory tract and kidneys and life-threatening due to the risk of renal- and respiratory failure;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Tavneos may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data from the pivotal clinical trial demonstrating that Tavneos was effective on top of standard of care in improving relevant clinical outcomes of granulomatosis with polyangiitis, including parameters of renal function and a relevant reduction of glucocorticoid treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tavneos, (2R,3S)-2-(4-Cyclopentylaminophenyl)-1-(2-fluoro-6-methylbenzoyl)piperidine-3-carboxylic acid(4-methyl-3-trifluoromethylphenyl)amide, avacopan for treatment of granulomatosis with polyangiitis (EU/3/14/1373) is not removed from the Community Register of Orphan Medicinal Products.