NEW DRUG APPROVAL

Brand Name	Tavneos™
Generic Name	avacopan
Drug Manufacturer	ChemoCentryx, Inc.

New Drug Approval

FDA Approval Date: October 07, 2021
Review Designation: Standard; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214487
Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) abbreviated EGPA, which was previously called the Churg-Strauss syndrome (CSS) or allergic granulomatosis and angiitis, is a multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia. EGPA is classified as a vasculitis of the small and medium sized arteries, although the vasculitis is often not apparent in the initial phases of the disease.

The most involved organ is the lung, followed by the skin. EGPA, however, can affect any organ system, including the cardiovascular, gastrointestinal, renal, and central nervous systems.

The relationship between antineutrophil cytoplasmic autoantibodies (ANCA) and granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), and "renal-limited" vasculitis (pauci-immune glomerulonephritis without evidence of extrarenal disease) is well established. ANCA are also present in a substantial subset (approximately 40 percent) of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome, abbreviated as EGPA). ANCA testing plays a critical role in the diagnosis and classification of vasculitides, even as debate about their ultimate importance in the pathogenesis and pathophysiology of these conditions continues.

The epidemiology of EGPA remains unclear because of the uncertainties related to diagnosis. Approximately 10 percent of patients with a major form of vasculitis are recognized to have EGPA. Among the three anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (EGPA, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis), EGPA is least common [5]. Prevalence in Europe ranges from 10.7 to 14/million. In the United States, the prevalence is approximately 18/million. The highest prevalence reported is from Australia, at 22.3 cases/million.

Efficacy

The efficacy and safety of Tavneos™ was evaluated in a double-blind, active-controlled, phase 3 clinical trial (NCT02994927) in 330 patients with newly diagnosed or relapsed ANCA associated vasculitis who were randomized 1:1 to one of the following treatment groups:

1. Tavneos™ (N=166): Patients received 30 mg avacopan twice daily for 52 weeks plus prednisone-matching placebo for 20 weeks.
2. Prednisone (N=164): Patients received avacopan-matched placebo twice daily for 52 weeks plus prednisone (tapered from 60 mg/day to 0 over 20 weeks).

All patients in both groups received one of the following standard immunosuppressive regimens:

- IV cyclophosphamide 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks followed by oral azathioprine 1 mg/kg/day with titration up to 2 mg/kg/day (or mycophenolate mofetil at a target dose of 2 g/day if azathioprine was contraindicated) from Week 15 onwards.
- Oral cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) for 14 weeks followed by azathioprine 1 mg/kg/day with titration up to 2 mg/kg/day (or mycophenolate mofetil at a target dose of 2 g/day if azathioprine was contraindicated) from Week 15 onwards.
- IV rituximab 375 mg/m2 once weekly for 4 weeks without azathioprine or mycophenolate mofetil.
- Glucocorticoids were allowed as pre-medication for rituximab to reduce hypersensitivity reactions, taper after glucocorticoids given during the Screening period, treatment of persistent vasculitis, worsening of vasculitis, or relapses, as well as for non-vasculitis reasons such as adrenal insufficiency.
- Randomization was stratified based on 3 factors: newly diagnosed or relapsing ANCA associated vasculitis, proteinase 3 positive or myeloperoxidase positive ANCA-associated vasculitis, and standard immunosuppressive regimen. The primary endpoints of the study were disease remission at Week 26 and sustained disease remission at Week 52. Disease remission was defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and no use of glucocorticoids for treatment of ANCA-associated vasculitis from Week 22 to Week 26.
- The two treatment groups were well balanced regarding baseline demographics and disease characteristics of patients in this trial. Approximately 65% of patients received rituximab, 31% received IV cyclophosphamide, and 4% received oral cyclophosphamide.

Remission at Week 26 and Sustained Remission at Week 52

Remission was achieved by 72.3% of patients in the Tavneos™ group and 70.1% of patients in the prednisone group at Week 26 (treatment difference: 3.4%, 95% CI [-6.0%, 12.8%]). At Week 52, a significantly higher percentage of patients had sustained remission in Tavneos™ group (65.7%) compared to the prednisone group (54.9%), as presented in Table.

Table 4: Sustained Remission at Week 52 in Phase 3 Trial (Intent-to-Treat Population)

	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)	Estimate of Treatment Difference	P-value[a]
Sustained Remission at Week 52	90 (54.9%)	109 (65.7%)	12.5%[b]	0.013
95% CI	(46.9, 62.6)[c]	(57.9, 72.8)[c]	(2.6, 22.3)[d]	

CI=confidence interval; N=number of patients in the analysis population for the specified treatment group; n=number of patients with disease remission; %=100*n/N

[a] 2-sided p-value of Summary Score Test (Agresti 2013)

[b] Summary Score estimate of the common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

[c] Clopper and Pearson exact CI

[d] Miettinen-Nurminen (Score) confidence limits for the common difference in remission rates

Safety

ADVERSE EVENTS

The most common adverse reactions (≥5%) are nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

WARNINGS & PRECAUTIONS

- Hepatotoxicity: Increase in liver function tests occurred in clinical trials. Obtain liver function tests before initiation of therapy and monitor as clinically indicated.
- Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial. Observe for signs and symptoms of angioedema and manage accordingly.
- Hepatitis B Virus (HBV) Reactivation: Cases of HBV reactivation occurred in a clinical trial. Withhold Tavneos™ and institute appropriate anti-infective therapy.
- Serious Infections: Avoid use of Tavneos™ in patients with active, serious infection, including localized infections.

CONTRAINDICATIONS

Serious hypersensitivity to avacopan or to any of the excipients.

Clinical Pharmacology

MECHANISMS OF ACTION

Avacopan is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a. It blocks C5a-mediated neutrophil activation and migration. The precise mechanism by which avacopan exerts a therapeutic effect in patients with ANCA-associated vasculitis has not been definitively established.

Dose & Administration

ADULTS

30 mg orally twice daily with food. It is taken along with standard therapy including glucocorticosteroids. It does not eliminate glucocorticoid use. Reduce dose to 30 mg orally, once daily in patients concomitantly receiving a strong CYP3A4 inhibitor.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustments are needed in patients with mild, moderate, or severe renal impairment.

HEPATIC IMPAIRMENT

No dosage adjustments are needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 10 mg.