Drug Monograph

Drug Name: **Tavneos™ (avacopan) capsule**
Drug Class: **Immunologic Agents: Complement Receptor Antagonist (C5aR)**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Tavneos is available in a 10 mg capsule.
Manufacturer:	Distributed by: ChemoCentryx, Inc., San Carlos, CA 94070.
Summary of Findings:	Tavneos was approved based on the results of a double-blind, active-controlled, Phase 3 clinical trial (ADVOCATE) with 330 participants who were newly diagnosed ANCA-associated vasculitis or had relapsed (54.8% GPA and 45.2% MPA). Patients were randomized 1:1 to Tavneos (n=166) or prednisone (n=164). All patients in the study also received a standard immunosuppressive regimen of intravenous (IV) rituximab (65%), IV cyclophosphamide (31%), or oral cyclophosphamide (4%). The primary endpoint of disease remission at Week 26 was achieved in 72.3% (n=120) of the avacopan group and in 70.1% (n=115) of the prednisone group (treatment difference: 3.4%, 95% CI [-6.0% to 12.8%]; *p<0.001* for noninferiority; *p=0.24* for superiority). Sustained remission at Week 52 was achieved in 65.7% (n=109) of the avacopan group and 54.9% (n=90) in the prednisone group (treatment difference: 12.5%, 95% CI [2.6% to 22.3%]; *p<0.001* for noninferiority; *p=0.007* for superiority). Tavneos was noninferior to prednisone taper for remission at Week 26 but superior with respect to sustained remission at Week 52.
Status Recommendation:	☒ Clinical Edit ☐ Open Access ☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required ☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

- ANCA-associated vasculitis (AAV) refers to a group of autoimmune disorders characterized by destruction and inflammation of small blood vessels; approximately 75% of patients have renal involvement (rapidly progressing glomerulonephritis). Diagnosis is frequently delayed as symptoms are not specific and multiple organ systems can be affected.
- AAV is caused by antibodies called ANCAs (Anti-Neutrophilic Cytoplasmic Autoantibodies) that target and attack neutrophils. When attached to neutrophils, ANCAs cause the neutrophil to attack small blood vessels in the body. There are 2 main kinds of autoantibodies that can be involved in AAV: proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA. These antibodies can be detected with an indirect immunofluorescence (IIF) utilizing alcohol-fixed buffy coat leukocytes or immunoassays such as enzyme-linked immunosorbent assay (ELISA). IIF are not antigen-specific, so use of immunoassays for screening is currently recommended. However, a small percentage of patients will not test positive for either autoantibody type; this is called “ANCA-negative” autoimmune vasculitis.
- Kidney involvement in AAV is common. A kidney biopsy is preferred, when possible, to confirm diagnosis; however, patients who are positive for ANCA should begin immunosuppressive therapy immediately while waiting for a biopsy. Despite a high rate of disease remission in AAV with therapy, the rate of end stage renal disease (ESRD) is around 8% at 6 months.
- Since small blood vessels are present throughout the body, AAV can cause a variety of symptoms. Clinical symptoms and microscopic findings have been used to group AAV into 3 subtypes based on frequency of organs involved, predominant autoantibody, rate of relapse, and clinical outcome:
    - Microscopic polyangiitis (MPA): Patients usually experience a range of symptoms such as kidney inflammation, skin lesions, and nerve damage, depending on which areas are affected. Weight loss and fevers frequently occur. Sometimes only the kidneys are affected, called “renal-limited ANCA vasculitis”. Patients with MPA are more likely to develop ESRD.
    - Granulomatosis with polyangiitis (GPA, previously called Wegner’s): Patients can experience blood vessel damage in various tissues, typically in the lungs, kidneys, and upper respiratory tract (nose, trachea, and ears). However, the inflammation is specifically caused by granulomas that form in the vasculature. GPA is the most common disease type.
    - Eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg-Strauss): This type of AAV is typically limited to the lungs and gastrointestinal tract, although other organs, like the heart and kidneys, may be affected. It is caused by granulomas primarily made up of eosinophils. Patients may experience asthma-like symptoms for many years before other symptoms of vasculitis appear. Only 40% of patients with EGPA produce detectable ANCA. Tavneos is not indicated for use in EGPA. Nucala® is currently the only FDA approved agent for EGPA.

	MPA	GPA	EGPA
Incidence per million person-years	1.5 - 16	1.9 - 13	0.8 - 4
ANCA-Positivity	~ 90%	~ 90%	~ 40%
PR3-ANCA	~ 25%	~ 75%	< 10%
MPO-ANCA	~ 60%	~ 20%	30-40%
Predominant Organ Involvement	Kidneys	Nose & sinuses, lungs, kidneys, joints, eyes	Lungs, upper airways, peripheral nerves, heart, skin
Rate of Renal Involvement	> 90%	~ 70 %	~ 25%
Rapidly progressive glomerulonephritis (RPGN)	~ 65%	~ 50%	< 15%

- AAV has an incidence of 200-400 cases per million people. An estimated 60,000 people in the United States have AAV. It is diagnosed most commonly in late middle age (50 to 60 years old).
- Prior to the use of high-dose glucocorticoids and cyclophosphamide, the mortality rate for patients with severe AAV was about 80% one year after diagnosis. The mortality rate has decreased substantially in recent years with the use of immunosuppressive therapies. The current estimated 5-year survival rate is 74-91% for GPA and 45-76% for MPA.
- Infections associated with immunosuppressive therapy are now the leading cause of death for patients with severe AAV in the first year of diagnosis, accounting for 34 - 48% of the mortality reported in some studies. Glucocorticoid therapy is also frequently cited as a major contributor to impaired quality of life for patients with AAV.

Dosage Form [3]

Tavneos is available in a 10 mg capsule.

Manufacturer [3]

Distributed by: ChemoCentryx, Inc., San Carlos, CA 94070.

Indication(s) [3]

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

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Tavneos is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a. Tavneos blocks C5a-mediated neutrophil activation and migration. Activation of the alternative complement pathway is believed to play a role in the pathogenesis for ANCA-associated vasculitis through terminal C5a production. C5a primes and activates neutrophils, which then release C5a when stimulated by inflammatory cytokines such as tumor necrosis factor (TNF) alpha. When activated by C5a, the C5aR becomes a potent neutrophil chemoattractant and agonist, increasing neutrophil adhesion, inducing neutrophil degranulation,

and producing reactive oxygen intermediates. C5aR activation also slow neutrophils' ability to transverse small blood vessels, particularly in the presence of ANCA, by decreasing neutrophil deformability. C5a also activates vascular endothelial cells, promoting their retraction and increased vascular permeability. Even with all the above, the precise mechanism by which Tavneos exerts a therapeutic effect in patients with ANCA-associated vasculitis has not been definitively established.

Pharmacokinetics:

Absorption	99% protein bound
Metabolism	Hepatic (CYP3A4); Active metabolite
Excretion	Fecal (77%), Renal (10%)
Half-life	Avacopan: 97.6 hours; Active metabolite: 55.6 hours

Clinical Trials Experience

STUDY 1 DESIGN (NCT01363388)	Randomized, double-blind, placebo-controlled Phase 2 CLEAR study
INCLUSION CRITERIA	• Clinical diagnosis of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis or renal limited vasculitis • Male and postmenopausal or surgically sterile female subjects aged at least 18 years with new or relapsed AAV where treatment with cyclophosphamide or rituximab would be required • Positive indirect immunofluorescence (IIF) test for perinuclear ANCA (P-ANCA) or cytoplasmic ANCA (C-ANCA), or positive ELISA test for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) at screening • Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min • Have at least one "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3
EXCLUSION CRITERIA	• Severe disease as determined by rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex or central nervous system involvement • Any other multi-system autoimmune disease • Medical history of coagulopathy or bleeding disorder • Received cyclophosphamide within 12 weeks of screening; if on azathioprine, mycophenolate mofetil or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1 • Received high-dose intravenous corticosteroids within 4 weeks of screening • On an oral dose of a corticosteroid of more than 10mg prednisone-equivalent at the time of screening • Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred; received anti-TNF treatment, abatacept, alemtuzumab, IVIg or plasma exchange within 12 weeks of screening
TREATMENT REGIMEN	Patients were randomized 1:1:1 to receive either placebo twice daily plus 60 mg prednisone daily, avacopan 30 mg twice daily plus 20 mg prednisone daily, or 30 mg avacopan twice daily without prednisone for 84 days.

RESULTS

Primary outcome: Proportion of subjects achieving at least 50% reduction in Birmingham Vasculitis Activity Score (BVAS) by Week 12 and no worsening in any body system (Vasculitis Damage Index [VDI]). Three subjects received rescue glucocorticoids during the treatment period: 1 in the control group and 2 in the avacopan without prednisone group. Lower incidence of glucocorticoid related adverse events in the treatment groups was primarily driven by a lower incidence of psychiatric disorders and new onset or worsening diabetes. At 12 weeks of follow-up, avacopan alone or with prednisone was shown to be noninferior to the control.

CLEAR (NCT01363388)	Placebo BID Plus 60 mg Prednisone (n=20)	Avacopan 30mg BID Plus 20 mg Prednisone (n=22)	Avacopan 30 mg BID Without Prednisone (n=21)
BVAS[1] Baseline			
Mean ± SEM	13.6 ± 1.4	14.3 ± 1.3	13.6 ± 1.4
BVAS Week 4			
Mean ± SEM	6.6 ± 1.2	4.9 ± 0.7	5.3 ± 1.3
% Change	-40 ± 12	-64 ± 5	-61 ± 9
P value	-	*P=0.04*	*P=0.04*
BVAS Week 12			
Mean ± SEM	5.0 ± 1.6	2.6 ± 0.7	3.6 ± 1.1
% Change	-56 ± 14	-79 ± 5	-73 ± 7
P value	-	*P=0.09*	*P=0.09*
VDI[2] Baseline			
Mean ± SEM	1.2 ± 0.3	0.9 ± 0.3	0.5 ± 0.3
VDI Week 12			
Mean ± SEM	1.8 ± 0.4	1.2 ± 0.3	0.8 ± 0.3
Change	0.7 ± 0.2	0.3 ± 0.1	0.2 ± 0.1
Remission (BVAS 0) at week 4 sustained through week 12			
no. (%)	1 (5%)	3 (14%)	6 (29%)
P value	-	*P=0.10*	*P=0.04*
Primary End Point: treatment response at week 12			
no. (%)	14 (70%)	19 (86.4%)	17 (81%)
P value – noninferiority	-	*P=0.002*	*P=0.01*
Patients with adverse effect potentially related to glucocorticoids			
no. (%)	15 (65%)	4 (18%)	11 (50%)

Abbreviations: SEM=standard error of the mean

[1] BVAS version 3 was used to capture vasculitis disease severity. Scoring ranges from 0 to 63, with higher scores meaning more severe disease activity. BVAS is used to score conditions that are directly attributable to vasculitis within the last 3 months and refers to current disease activity.

[2] VDI is used to record any condition that has occurred and lasted for at least 3 months since the start of vasculitis and refers to chronic damage whether it has anything to do with vasculitis. Scoring ranges from 0 to 64. VDI is a cumulative measure of damage, so the score never improves but either remains the same or gets worse. A total VDI score of > 4 significantly increases the risk of mortality at 2 years.

SAFETY

Discussed in the Adverse Effects section below.

STUDY 2 DESIGN (NCT02222155)	Phase 2 randomized, double-blind, placebo-controlled CLASSIC study
INCLUSION CRITERIA	• Clinical diagnosis of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis or renal limited vasculitis • Male and female subjects, aged at least 18 years, with new or relapsed AAV where treatment with cyclophosphamide or rituximab would be required

	• Use of adequate contraception during, and for at least the three months after, any administration of study medication is required • Positive indirect immunofluorescence (IIF) test for P-ANCA or C-ANCA, or positive ELISA test for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) at screening • Have at least one "major" item, or at least 3 other items, or at least 2 renal items on the Birmingham Vasculitis Activity Score (BVAS) version 3 • Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min
EXCLUSION CRITERIA	• Severe disease as determined by rapidly progressive glomerulonephritis, alveolar hemorrhage, hemoptysis, rapid-onset mononeuritis multiplex or central nervous system involvement • Any other multi-system autoimmune disease • Medical history of coagulopathy or bleeding disorder • Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1 • Received intravenous corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to screening • Received an oral daily dose of a corticosteroid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit • Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred; received anti-tumor necrosis factor (TNF) treatment, abatacept, alemtuzumab, intravenous immunoglobulin (IVIg), belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening
TREATMENT REGIMEN	Three arms: • Avacopan 10 mg twice daily for 12 weeks plus SOC (n=13) • Avacopan 30 mg twice daily for 12 weeks plus SOC (n=16) • Placebo twice daily for 12 weeks plus SOC (n=13)
RESULTS	The safety and efficacy of 2 different dosage regimens of avacopan plus SOC[1] vs. SOC only. The addition of avacopan to SOC was well tolerated, with similar rates of adverse events across all arms. There may be a potential clinical benefit with the addition of avacopan 30 mg to SOC. Early disease remission, renal response in patients with hematuria and albuminuria, renal function (eGFR), and patient quality of life assessments were all higher in the avacopan 30 mg arm.
SAFETY	Discussed in the Adverse Effects section below.

Abbreviations: SOC=standard of care

[1] Standard of Care= combination of high-dose glucocorticoids (60mg/day prednisone steadily tapering to 10 mg/day by Week 11 and 0 mg/day by Week 20) and either cyclophosphamide or rituximab

STUDY 3 DESIGN (NCT02994927)	Double-blind, active-controlled, Phase 3 ADVOCATE study (N=330)
INCLUSION CRITERIA	• Clinical diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis • Male and female subjects, aged at least 18 years, with newly diagnosed or relapsed AAV where treatment with cyclophosphamide or rituximab is needed; where approved by Regulatory Agencies, adolescents (12-17 years old) may be enrolled

	• Use of adequate contraception • Positive test for anti-PR3 or anti-MPO • At least 1 major item, or at least 3 non-major items, or at least the 2 renal items of proteinuria and hematuria on BVAS • Estimated glomerular filtration rate ≥15 mL/min/1.73 m^2 at screening
EXCLUSION CRITERIA	• Pregnant or breast-feeding • Alveolar hemorrhage requiring pulmonary ventilation support at screening • Any other known multi-system autoimmune disease • Required dialysis or plasma exchange within 12 weeks prior to screening • Have a kidney transplant • Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate mofetil or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1 • Received intravenous glucocorticoids, >3000 mg methylprednisolone equivalent, within 4 weeks prior to screening • Have been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening • Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count > $0.01x10^9$/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening • For patients scheduled to receive cyclophosphamide treatment, urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count <50,000/µL before start of dosing • Participated previously in a CCX168 study
TREATMENT REGIMEN	Patients were randomized 1:1 to one of the following groups: • Avacopan group (N=166)- patients receive 30 mg twice daily for 52 weeks plus prednisone-matching placebo for 20 weeks • Prednisone group (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 received standard immunosuppressive regimens of IV cyclophosphamide (31%), oral cyclophosphamide (4%), or IV rituximab (65%) with follow-up therapy of oral azathioprine or mycophenolate mofetil. Glucocorticoid therapy during the screening period had to be tapered to 20 mg or less of prednisone equivalent before beginning the trial, then further tapered to discontinuation by the end of Week 4. Patients with worsening disease that involved a major item in the BVAS could be treated with rescue glucocorticoid therapy.

RESULTS

Primary efficacy end points:

- Clinical Remission (CR) at week 26 defined as a BVAS of 0 and no receipt of glucocorticoids for 4 weeks before Week 26
- Sustained Remission (SR) defined as remission at Week 26 and at Week 52 with no receipt of glucocorticoids for 4 weeks before Week 52. Patients were not considered in SR if they had remission at Week 26 but a relapse thereafter.

Key Secondary End Points:

- Glucocorticoid toxic effects according to the Glucocorticoid Toxicity Index (GTI) during the first 26 weeks as measured by the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS)
  - Cumulative Worsening Score (GTI-CWS) – ranges from 0 to 410
  - Aggregate Improvement Score (GTI-AIS) – ranges from -317 to 410
  - For both scales higher scores indicate greater severity of toxic effects
- Change from baseline in health-related quality of life
  - 36-Item Short Form Survey (SF-36), version 2
  - EuroQol Group 5-Dimensions 5-Level Questionnaire (ED-5D-5L)
  - Range 0-100 for both, with higher scores indicating better quality of life
- Change from baseline in eGFR and urinary albumin:creatinine ratio

ADVOCATE (NCT02994927)	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary End Points			
Remission at week 26, no. (%)	120 (72.3)	115 (70.1)	3.4 (-6.0 to 12.8) Noninferiority P value < 0.001 Superiority P value = 0.24
Sustained remission at week 52, no. (%)	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3) Noninferiority P value < 0.001 Superiority P value = 0.007
Secondary End Points			
GTI-CWS			
Week 13			
Patients Evaluated	160	161	
Least-squares mean	25.7 ± 3.4	36.6 ± 3.4	-11.0 (-19.7 to -2.2)
Week 26			
Patients Evaluated	154	153	
Least-squares mean	39.7 ± 3.4	56.6 ± 3.4	-16.8 (-25.6 to -8.0)
GTI-AIS			
Week 13			
Patients Evaluated	160	161	
Least-squares mean	9.9 ± 3.4	23.2 ± 3.5	-13.3 (-22.2 to -4.4)
Week 26			
Patients Evaluated	154	153	
Least-squares mean	11.2 ± 3.5	23.4 ± 3.5	-12.1 (-21.1 to -3.2)
eGFR – ml/min/1.73 m^2 *			
Baseline			
Patients Evaluated	131	134	
Mean	44.6 ± 2.4	45.6 ± 2.4	
Change from baseline to week 26			
Patients Evaluated	121	127	
Least-squares mean	5.8 ± 1.0	2.9 ± 1.0	2.9 (0.1 to 5.8)
Change from baseline to week 52			
Patients Evaluated	119	125	

Least-squares mean	7.3 ± 1.0	4.1 ± 1.0	3.2 (0.3 to 6.1)
SF-36 physical component score			
Baseline			
Patients Evaluated	165	160	
Mean	39.2 ± 0.8	40.1 ± 0.8	
Change from baseline to week 26			
Patients Evaluated	153	147	
Least-squares mean	4.45 ± 0.73	1.34 ± 0.74	3.10 (1.17 to 5.03)
Change from baseline to week 52			
Patients Evaluated	147	144	
Least-squares mean	4.98 ± 0.74	2.63 ± 0.75	2.35 (0.40 to 4.31)
Score on EQ-5D-5L visual-analogue scale			
Baseline			
Patients Evaluated	166	162	
Mean	65.8 ± 1.5	63.4 ± 1.8	
Change from baseline to week 26			
Patients Evaluated	153	150	
Least-squares mean	9.1 ± 1.4	5.5 ± 1.4	3.6 (-0.1 to 7.2)
Change from baseline to week 52			
Patients Evaluated	149	146	
Least-squares mean	13.0 ± 1.4	7.1 ± 1.4	5.9 (2.3 to 9.6)
Urinary albumin:creatinine ratio **			
Baseline			
Patients Evaluated	125	128	
Geometric mean (range)	433 (20-6461)	312 (11-5367)	
Percent change from baseline to week 4			
Patients Evaluated	121	124	
Least-squares mean ± SE	-40 ± 10	0 ± 9	-40 (-53 to -22)
Percent change from baseline to week 13			
Patients Evaluated	116	121	
Least-squares mean ± SE	-55 ± 10	-49 ± 9	-12 (-32 to 13)
Percent change from baseline to week 26			
Patients Evaluated	113	118	
Least-squares mean ± SE	-63 ± 10	-70 ± 10	25 (-3 to 61)
Percent change from baseline to week 52			
Patients Evaluated	109	114	
Least-squares mean ± SE	-74 ± 10	-77 ± 10	12 (-14 to 45)

*In patients with renal disease at baseline based on the BVAS
**in patients with renal disease at baseline based on the BVAS and a urinary albumin:creatinine ratio of at least 10 at baseline. Percent changes from baseline are based on ratios of geometric means of visit over baseline.

Results:

- Avacopan was noninferior, but not superior, to tapered prednisone for remission at week 26
- Avacopan was superior to tapered prednisone for sustained remission at week 52
- There was a greater incidence of glucocorticoid induced toxic effects in the prednisone group
- Positive effects of avacopan on eGFR and albuminuria were seen; this may be due to blockade in the glomeruli of the C5a-C5aR axis, arresting the potent chemoattraction and activation of neutrophils that damage the glomeruli
- Quality of life improved in both treatment groups

Notes:

- Glucocorticoids were used by patients in the avacopan group. Mean total prednisone-equivalent dose of oral and IV glucocorticoids:
  - Avacopan group: 1,349 mg (4 mg per patient per day)

	○ Prednisone group: 3,655 mg (12 mg per patient per day) • Nine patients in the avacopan group and 6 in the prednisone group had an abnormality on liver-function testing. All events resolved with the withdrawal of trial and other potentially hepatotoxic medications. • Incidence of glucocorticoid related adverse events (based on European League against Rheumatism criteria) ○ Avacopan group: 66.3% ○ Prednisone group: 80.5% • Findings on all secondary endpoints were not included in the final package insert • The FDA's Arthritis Advisory Committee reviewed avacopan on May 6, 2021. The committee voted 9 to 9 that the efficacy data support approval and 10 to 8 that safety data support its approval. The final vote on whether the overall benefit-risk profile supported avacopan approval was 10 to 8 in favor. ○ Concerns were raised that ADVOCATE was attempting to demonstrate efficacy of both remission induction and remission maintenance, which many believed should have been split into 2 separate studies ○ No patients received rituximab maintenance therapy in ADVOCATE; however, the indication was not approved at study design. Concerns were raised that the study no longer reflected the addition of avacopan to standard of care. ○ Concerns were raised on the potential confounding effects of the use of non-study supplied glucocorticoids in both treatment arms as well as potential differences in the cyclophosphamide and rituximab standard treatment groups ○ Concerns were raised about the safety of avacopan, especially with respect to liver toxicity.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- Hypersensitivity

Warnings and Precautions [3,4]

- Hepatoxicity
  - A high incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events, occurred in clinical trials
  - Obtain liver function tests (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiation of therapy, every 4 weeks for the first 6 months of therapy, and as clinically indicated thereafter
- Serious Hypersensitivity Reactions
  - In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization
  - Observe for signs and symptoms of angioedema and manage accordingly
- Hepatitis B Virus (HBV) Reactivation
  - Cases of HBV reactivation, including life threatening hepatitis B, occurred in clinical trials. Before initiating therapy, screen for HBV infection by measuring HBsAg and

anti-HBc.
    - Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for six months following therapy.
    - For patients who develop reactivation of HBV, withhold Tavneos and begin appropriate anti-infective therapy
- Serious Infections
    - Serious, including fatal, infections occurred in clinical trials. The most common were pneumonia and urinary tract infections.
    - Avoid use in patients with active, serious infections, including localized infections
    - Consider the risks and benefits of therapy prior to initiation of Tavneos therapy in patients:
        - With chronic or recurrent infection
        - Who have been exposed to tuberculosis
        - With a history of serious or opportunistic infection
        - Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses
        - With underlying conditions that predispose them to infection

Adverse Effects [3,4]

Most common, ≥5%	Tavneos (N=166) n (%)	Prednisone (N=164) n (%)
Nausea	39 (23.5)	34 (20.7)
Headache	34 (20.5)	23 (14.0)
Hypertension	30 (18.1)	29 (17.7)
Diarrhea	25 (15.1)	24 (14.6)
Vomiting	25 (15.1)	21 (12.8)
Rash	19 (11.4)	13 (7.9)

Drug Interactions [3,4]

- Strong and moderate CYP3A4 inducers (i.e., rifampin): avoid use
- Strong CYP3A4 inhibitors (i.e., itraconazole): reduce dose to 30 mg once daily
- Sensitive CYP3A4 substrates: monitor for adverse reactions and consider dose reduction of sensitive substrates with narrow therapeutic windows

Dosage and Administration [3,4]

- Tavneos is dosed 30 mg (3 capsules) twice daily with food.
- Reduce dose to 30 mg once daily when used concomitantly with strong CYP3A4 inhibitors.
- Capsules should not be crushed, chewed, or opened.
- If a dose is missed, the patient should wait until the next usual scheduled time to take the next dose. Do not double the dose.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Avacopan	Tavneos™	ChemoCentryx	30 mg orally twice daily with food	$14,448 per 30 days
Rituximab	Rituxan (and biosimilars)	Various	Induction: 375 mg/m^2 IV once weekly for 4 weeks Maintenance: 500 mg IV every 2 weeks for 2 doses, then 500 mg IV every 6 months based on clinical evaluation (Given with glucocorticoids)	$3,600-$4,700 per 500 mg dose

** Wholesale Acquisition Cost

Conclusion

Tavneos is the first FDA approved orally administered inhibitor of the complement C5a receptor and represents the first new drug for AAV in the past decade. ANCA-associated vasculitis is thought to be caused by an over-activation of the complement system, which causes generation of complement fragment 5a (C5a). C5a levels are increased in patients with ANCA-associated vasculitis. Tavneos can selectively block the C5a receptor. Tavneos is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a. Tavneos blocks C5a-mediated neutrophil activation and migration. Tavneos was approved based on the results of a double-blind, active-controlled, Phase 3 clinical trial (ADVOCATE), which enrolled 330 patients with newly diagnosed or relapsed ANCA-associated vasculitis (54.8% GPA and 45.2% MPA). Tavneos was noninferior to prednisone taper for remission at Week 26 but superior with respect to sustained remission at Week 52. Tavneos carries a warning for hepatoxicity evidenced by abnormal liver function tests during the ADVOCATE trial. Common adverse reactions that occurred in the avacopan group included nausea, headache, hypertension, diarrhea, vomiting, rash, and fatigue.

Recommendation

The MO Healthnet Division recommends adding this drug to a Tavneos clinical edit.

References

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Prepared by: Jennifer Colozza, PharmD; April Ash, PharmD

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