

TAVNEOS- avacopan capsule

ChemoCentryx, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAVNEOS safely and effectively. See full prescribing information for TAVNEOS.

TAVNEOS® (avacopan) capsules, for oral use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

TAVNEOS is a complement 5a receptor (C5aR) antagonist indicated as an 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. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is 30 mg (three 10 mg capsules) twice daily, with food. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg (3)

CONTRAINDICATIONS

Serious hypersensitivity to avacopan or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Increase in liver function tests occurred in clinical trials. Obtain liver function tests before initiation of therapy and monitor as clinically indicated. (5.1)
- Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial. Observe for signs and symptoms of angioedema and manage accordingly. (5.2)
- Hepatitis B Virus (HBV) Reactivation: Cases of HBV reactivation occurred in a clinical trial. Withhold TAVNEOS and institute appropriate anti-infective therapy. (5.3)
- Serious Infections: Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. (5.4)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) are: nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Strong and moderate CYP3A4 enzyme inducers: Avoid use. (7.1)
- Strong CYP3A4 enzyme inhibitors: Reduce avacopan dose to 30 mg once daily. (7.2)
- CYP3A4 substrates: Consider dose reduction of CYP3A4 substrates when co-administering TAVNEOS with CYP3A4 substrates. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TAVNEOS is indicated as an 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluations Prior to Treatment Initiation

Before initiating TAVNEOS, perform the following evaluations:

- Liver Function Tests: Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS. TAVNEOS is not recommended for use in patients with cirrhosis, especially those with severe hepatic impairment (Child-Pugh C) [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.7)*].
- Hepatitis B (HBV) Serology: Screen patients for HBV infection by measuring HBsAg and anti-HBc. For patients with evidence of prior or current HBV infection, consult with a physician with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before or during treatment with TAVNEOS [see *Warnings and Precautions (5.3)*].

2.2 Recommended Dosage and Administration

The recommended dose of TAVNEOS is 30 mg (three 10 mg capsules) twice daily, with food.

Advise patients that TAVNEOS capsules should not be crushed, chewed or opened.

If a dose is missed, instruct the patient to wait until the usual scheduled time to take the next regular dose. Instruct the patient not to double the next dose.

2.3 Dosage Modifications Due to CYP3A4 Inhibitors

Reduce the dosage of TAVNEOS to 30 mg once daily when used concomitantly with strong CYP3A4 inhibitors.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, opaque, yellow and light orange with CCX168 printed in black.

4 CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reaction to avacopan or to any of the excipients [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events [see *Adverse Reactions 6.1*].

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out [*see Adverse Reactions (6.1)*].

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering TAVNEOS to a patient with liver disease. Monitor patients closely for hepatic adverse reactions [*see Use in Specific Populations (8.7)*].

5.2 Hypersensitivity Reactions

TAVNEOS may cause angioedema [*see Adverse Reactions (6.1)*]. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

5.3 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

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 TAVNEOS therapy.

In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

5.4 Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were

pneumonia and urinary tract infections.

Avoid use of TAVNEOS in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses;
or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hepatotoxicity [*see Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.2)*]
- Hepatitis B Virus (HBV) Reactivation [*see Warnings and Precautions (5.3)*]
- Serious Infections [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because the clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone [*see Clinical Studies (14)*]. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and

2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in $\geq 5\%$ of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1. Adverse Reactions Reported in $\geq 5\%$ of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

| Adverse Reaction | Prednisone (N = 164) n (%) | TAVNEOS (N = 166) n (%) |
|----------------------------|---|--|
| Nausea | 34 (20.7) | 39 (23.5) |
| Headache | 23 (14.0) | 34 (20.5) |
| Hypertension | 29 (17.7) | 30 (18.1) |
| Diarrhea | 24 (14.6) | 25 (15.1) |
| Vomiting | 21 (12.8) | 25 (15.1) |
| Rash | 13 (7.9) | 19 (11.4) |
| Fatigue | 15 (9.1) | 17 (10.2) |
| Upper abdominal pain | 10 (6.1) | 11 (6.6) |
| Dizziness | 10 (6.1) | 11 (6.6) |
| Blood creatinine increased | 8 (4.9) | 10 (6.0) |
| Paresthesia | 7 (4.3) | 9 (5.4) |

N = number of patients randomized to treatment group in the Safety Population; n = number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin [see *Clinical Pharmacology (12.3)*]. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

7.2 CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole [see *Clinical Pharmacology (12.3)*]. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

7.3 CYP3A4 Substrates

Avacopan is a moderate CYP3A4 inhibitor. Co-administration of avacopan and 40 mg simvastatin increases the systemic exposure of simvastatin. While taking TAVNEOS, limit simvastatin dosage to 10 mg daily (or 20 mg daily for patients who have previously tolerated simvastatin 80 mg daily for at least one year without evidence of muscle toxicity). Consider dose reduction of CYP3A4 substrates when co-administering TAVNEOS with CYP3A4 substrates. Consult the concomitant CYP3A4 substrate product information when considering administration of such products together with TAVNEOS [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD (see *Animal Data*).

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams (see *Animal Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters. [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of TAVNEOS in pediatric patients have not been established.

8.5 Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis [see *Clinical Studies (14)*], 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

8.6 Patients with Renal Impairment

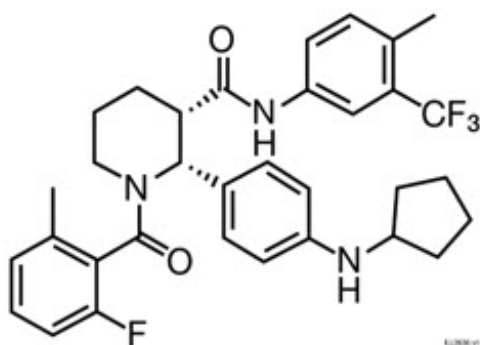
No dose adjustment is required for patients with mild, moderate, or severe renal impairment [see *Clinical Pharmacology (12.3)*]. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

8.7 Patients with Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment [*Clinical Pharmacology (12.3)*]. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

11 DESCRIPTION

TAVNEOS (avacopan) capsules contain avacopan, a C5aR antagonist. Avacopan is a chiral molecule containing two stereocenters and has a chemical name of (2*R*,3*S*)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-*N*-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide. It has a molecular formula of C₃₃H₃₅F₄N₃O₂ and a molecular weight of 582 g/mol. Avacopan has the following structural formula:



Avacopan is a white to pale yellow crystalline solid that is soluble in organic solvents and practically insoluble in water.

TAVNEOS is available as a 10 mg capsule for oral administration. The capsules include the following inactive ingredients: Polyethylene glycol 4000 (PEG-4000), Polyoxyl-40 hydrogenated castor oil. The capsules are a light orange and yellow opaque bicolor gelatin capsule with a clear gelatin sealing band. The top half of the capsule is printed with "CCX168" in black ink. The capsule shell contains gelatin, red iron oxide, yellow iron oxide, and titanium dioxide, and the capsule sealing band contains gelatin and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Avacopan is a complement 5a receptor (C5aR) antagonist that inhibits the interaction between C5aR and the anaphylatoxin C5a. Avacopan 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.

12.2 Pharmacodynamics

Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. The clinical significance of the pharmacodynamic effect is unclear.

Cardiac Electrophysiology

At the approved recommended dose, TAVNEOS does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Based on population pharmacokinetic analysis, the mean steady state plasma exposure estimates of avacopan are 3466 ± 1921 ng•h/mL for the 12-hour area under the plasma drug concentration over time curve (AUC_{0-12hr}) and 349 ± 169 ng/mL for the maximum plasma concentration (C_{max}) in patients with ANCA-associated vasculitis receiving 30 mg avacopan twice daily. Steady state plasma levels of avacopan are reached by 13 weeks and the accumulation is approximately 4-fold.

Absorption

Co-administration of 30 mg in capsule formulation with a high-fat, high-calorie meal increases AUC and C_{max} of avacopan by approximately 72% and 8%, respectively, and delays t_{max} by approximately 4 hours (from 2.0 hours to 6.0 hours).

Distribution

The 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 of avacopan is estimated to be 345 L.

Elimination

Based on population pharmacokinetic analysis, the estimated total apparent body clearance (CL/F) of avacopan is 16.3 L/h. Following a single dose of 30 mg avacopan with food, the mean elimination half-lives of avacopan and M1 are 97.6 hours and 55.6 hours, respectively, in healthy subjects.

Metabolism

CYP3A4 is the major enzyme responsible for the clearance of avacopan and for the formation and clearance of the major circulating metabolite M1, a mono-hydroxylated product of avacopan. M1 was present at ~12% of the total drug-related materials in plasma and has approximately the same activity as avacopan on the C5aR.

Excretion

The main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into feces. Following oral administration of radiolabelled avacopan, about 77% and 10% of the radioactivity was recovered in feces and urine, respectively, and 7% and <0.1% of the radioactive dose was recovered as unchanged avacopan in feces and urine, respectively.

Specific Populations

No clinically significant differences in plasma exposure of avacopan and metabolite M1 were observed based on race (White, Asian, Black), gender (female 31%), age (18 to 83 years), body weight (40.3-174 kg), and renal function (eGFR 14-170 mL/min/1.73 m² at baseline).

Patients with Hepatic Impairment

Mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment had no clinically relevant effect on avacopan and M1 plasma exposure. In subjects with mild or moderate hepatic impairment, avacopan AUC increased by 12% and 12%, respectively, C_{max} decreased by 13% and 17%, respectively, compared to subjects with normal liver function. In subjects with mild or moderate hepatic impairment, M1 AUC increased by 11% and 18%, respectively, C_{max} decreased by 5% and 16%, respectively, compared to subjects with normal liver function.

TAVNEOS has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies

Effects of Other Drugs on TAVNEOS

Avacopan is primarily metabolized by CYP3A4. *In vitro* studies indicate that avacopan is not a substrate of BCRP and P-gp efflux, and OATP1B1 and OATP1B3 uptake transporters. M1 is a substrate of P-gp but is not a substrate of BCRP efflux, and OATP1B1 and OATP1B3 uptake transporters. Summary of results from a clinical study which evaluated the effect of co-administered drugs on avacopan and M1 plasma exposures is shown in Table 2.

Table 2. Changes in Pharmacokinetics of Avacopan and M1 in the Presence of Co-administered Drugs

| Co-administered Drug | Regimen of Co-administered Drug | Ratio (90% CI)* | | |
|--|----------------------------------|-----------------|----------------------|----------------------|
| | | | C _{max} | AUC |
| Strong CYP3A4 inhibitor: itraconazole | 200 mg once daily for 4 days | Avacopan | 1.87 (1.70, 2.06) | 2.19 (2.00, 2.41) |
| | | M1 | 1.03 (0.95, 1.11) | 1.19 (1.11, 1.28) |
| Strong CYP3A4 inducer: rifampin | 600 mg once daily for 11 days | Avacopan | 0.21 (0.18, 0.25) | 0.07 (0.06, 0.10) |
| | | M1 | 0.27 (0.23, 0.31) | 0.07 (0.06, 0.09) |

CI: Confidence interval

* Ratios for C_{max} and AUC comparing co-administration of the medication with avacopan vs. administration of avacopan alone.

Proton-pump inhibitors such as omeprazole are not expected to have a clinically relevant effect on avacopan plasma exposure.

Effect of TAVNEOS on Other Drug Substances

In vitro studies indicate that avacopan does not inhibit CYP1A2, CYP2B6, CYP2C8,

CYP2C9, CYP2C19, and CYP2D6, and does not induce CYP1A2 and CYP2B6, but shows induction and time-dependent inhibition of CYP3A4. *In vitro* studies indicate that M1 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6, and has a low potential to induce CYP3A4, CYP1A2 and CYP2B6, but may inhibit CYP2C9 and CYP3A4.

In vitro studies indicate that avacopan and M1 do not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations.

Summary of results from clinical studies which evaluated the effect of avacopan on other drugs is shown in Table 3.

Table 3. Change in Pharmacokinetics of Co-administered Drugs in the Presence of Avacopan

| Co-administered Drug | Regimen of Avacopan | Ratio (90% CI)* | |
|---|---|----------------------|----------------------|
| | | C _{max} | AUC |
| Sensitive CYP3A4 substrate: simvastatin | 60 mg twice daily for 7 days (fed) [†] | 3.20 (2.49, 4.10) | 3.53 (3.23, 3.85) |
| Sensitive CYP3A4 substrate: midazolam | 30 mg twice daily for 11 days (fasted) [‡] | 1.55 (1.41, 1.69) | 1.81 (1.65, 1.98) |
| Sensitive CYP2C9 substrate: celecoxib | 30 mg twice daily for 11 days (fasted) [‡] | 1.64 (1.34, 2.00) | 1.15 (1.03, 1.28) |

CI: Confidence interval

* Ratios for C_{max} and AUC comparing co-administration of the medication with avacopan vs. administration of medication alone.

† Avacopan doses were taken with food. Avacopan systemic exposure represents the therapeutic exposure at steady state with 30 mg twice daily under fed conditions.

‡ Avacopan doses were taken under fasted conditions. No food was allowed for at least 2 hours post dose for the morning doses. Avacopan systemic exposure was below the therapeutic exposure at steady state with 30 mg twice daily under fed conditions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in Sprague-Dawley rats and Syrian hamsters were conducted to assess the carcinogenic potential of avacopan. Avacopan demonstrated no tumorigenic potential in a study with rats that received oral doses up to 100 mg/kg/day (approximately 3 times the MRHD in adults on an AUC basis) and a study in hamsters that received oral doses up to 100 mg/kg/day (approximately 6 times the MRHD in adults on an AUC basis).

Mutagenesis

Avacopan was not mutagenic or clastogenic in the following assays: *in vitro* bacterial reverse mutation (Ames) test, *in vitro* mouse lymphoma assay, and *in vivo* rat micronucleus test.

Impairment of Fertility

Fertility and reproductive performance were unaffected in male and female hamsters

that received avacopan by the oral route at dose levels up to 1000 mg/kg/day (approximately 7 times the MRHD on an AUC basis).

14 CLINICAL STUDIES

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 group (N = 166): Patients received 30 mg avacopan twice daily for 52 weeks plus prednisone-matching placebo for 20 weeks
2. 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 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. Sustained remission was defined as remission at Week 26 and remission at Week 52, without relapse between Week 26 and Week 52. Remission at Week 52 was defined as BVAS of 0 and no use of glucocorticoids for treatment of ANCA-associated vasculitis from Week 48 to Week 52. Relapse was defined as occurrence of one major item, at least 3 non-major items, or 1 or 2 non-major items for at least 2 consecutive visits on the BVAS after remission (BVAS of 0) had been achieved.

The two treatment groups were well balanced regarding baseline demographics and disease characteristics of patients in this trial. The mean patient age was 60.9 years. Most patients were male (56.4%), Caucasian (84.2%), and had newly diagnosed disease (69.4%). Patients had either GPA (54.8%) or MPA (45.2%) and had presence of anti-PR3 (43.0%) or anti-MPO (57.0%) antibodies. Mean baseline BVAS was 16.2; patients most commonly had manifestations within the renal component (81.2%), general component

(68.2%), ear/nose/throat component (43.6%), and chest component (43.0%). 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 4.

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* |
|---|---|--|---|----------------------|
| Sustained Remission at Week 52 | 90 (54.9%) | 109 (65.7%) | 12.5% [†] | 0.013 |
| 95% CI | (46.9, 62.6) [‡] | (57.9, 72.8) [‡] | (2.6, 22.3) [§] | |

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

* 2-sided p-value of Summary Score Test (Agresti 2013)

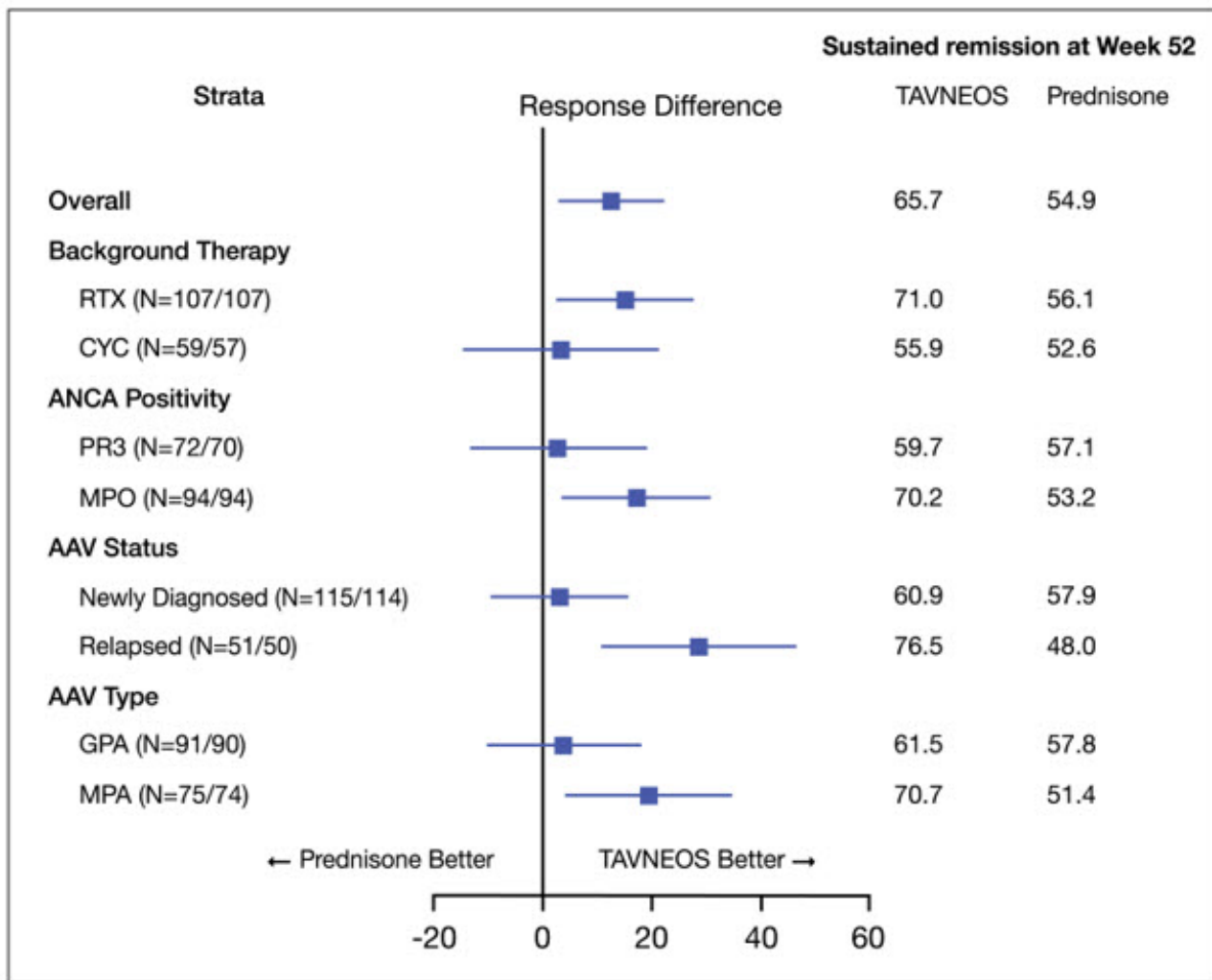
† Summary Score estimate of the common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

‡ Clopper and Pearson exact CI

§ Miettinen-Nurminen (Score) confidence limits for the common difference in remission rates

In pre-specified subgroup efficacy analyses, sustained remission at 52 weeks in patients was examined based on stratification factors and GPA/MPA disease. The results are displayed in Figure 1 below.

Figure 1. Forest Plot of Sustained Remission at Week 52 Based on Disease Related Variables



AAV = ANCA-associated vasculitis, CYC = cyclophosphamide, GPA = granulomatosis with polyangiitis, MPA = microscopic polyangiitis; MPO = myeloperoxidase positive, PR3 = anti-proteinase 3 positive, and RTX = rituximab. The treatment difference between TAVNEOS and prednisone groups is presented with point estimate and 95% confidence interval using normal approximation. The notation N = XXX/YYY indicates the number of patients randomized who received at least one dose of drug in TAVNEOS arm and prednisone arm, respectively. Subgroup findings should be interpreted with caution due to small sample sizes and overlapping subgroups.

16 HOW SUPPLIED/STORAGE AND HANDLING

TAVNEOS (avacopan) capsule is supplied as a 10 mg, hard, opaque yellow and light orange capsule with "CCX168" printed in black.

- Bottle containing 180 capsules with child resistant induction seal closure (NDC 73556-168-01)
- Bottle containing 30 capsules with child resistant induction seal closure (NDC 73556-168-02)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Do not use if seal is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Dosage and Administration: Instruct the patient that TAVNEOS should be swallowed whole. TAVNEOS should not be chewed or crushed. If a dose is missed, instruct the patient to take the next scheduled dose [see *Dosage and Administration (2.2)*].
- Hypersensitivity Reactions: Advise patients to seek immediate medical attention when experiencing any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, and difficulty in swallowing or breathing) and to discontinue the drug until they have consulted with the prescribing physician [see *Warnings and Precautions (5.2)*].
- Hepatotoxicity: Inform patients of the signs and symptoms of hepatic adverse reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of liver problems; yellowing of the skin or the white part of the eyes (jaundice), dark or brown (tea colored) urine, pain on the upper right side of the stomach area (abdomen), bleeding or bruising [see *Warnings and Precautions (5.1)*].
- Infections: Inform patients that serious infections have been reported in patients receiving TAVNEOS, including reactivation of hepatitis B infection. Instruct patients to contact their healthcare provider immediately if they develop any signs or symptoms of an infection [see *Warnings and Precautions (5.4)*].
- Lactation: Consider benefits/risk during lactation [see *Use in Specific Populations (8.2)*].

TAVNEOS® (avacopan)

Manufactured for:

ChemoCentryx, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Patent: <https://pat.amgen.com/tavneos>

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| |
|---|
| <p style="text-align: center;">MEDICATION GUIDE TAVNEOS® (tav' nee ose) (avacopan) capsules, for oral use</p> |
| <p>What is the most important information I should know about TAVNEOS? TAVNEOS may cause serious side effects, including:</p> <ul style="list-style-type: none">• Liver problems. People taking TAVNEOS may have serious liver problems. Call your healthcare provider right away if you have unexplained symptoms such as:<ul style="list-style-type: none">◦ yellowing of your skin or the white part of your eyes (jaundice)◦ pain on the upper right side of your stomach area (abdomen)◦ dark or brown (tea colored) urine◦ bleeding or bruising more easily than normal◦ loss of appetite |

- feeling tired

◦ loss of appetite

Your healthcare provider will do blood tests to check how well your liver is working before starting and during your treatment with TAVNEOS.

What is TAVNEOS?

- TAVNEOS is a prescription medicine that is used with other medicines (such as glucocorticoids) to treat adults with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)- associated vasculitis (granulomatosis with polyangiitis [GPA], formerly known as Wegener's granulomatosis, and microscopic polyangiitis [MPA]).

It is not known if TAVNEOS is safe and effective in children under the age of 18.

Do not take TAVNEOS:

- if you are allergic to avacopan or any of the other ingredients in TAVNEOS. See the end of this Medication Guide for a complete list of the ingredients in TAVNEOS.
 - Get medical help right away if you experience swollen lips, tongue, throat, trouble swallowing, or difficulty breathing. These could be signs of an allergic reaction. **Do not** take more of TAVNEOS until you have consulted with your healthcare provider.

Before taking TAVNEOS, tell your healthcare provider about all your medical conditions including if you:

- have or have had abnormal liver blood tests.
- have or have had liver problems.
- have or think you may have hepatitis B or hepatitis C.
- have an infection.
- are pregnant or are planning to become pregnant. It is not known if TAVNEOS will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if TAVNEOS can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TAVNEOS.

Tell your healthcare provider about all the other medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TAVNEOS and certain other medicines may affect each other and cause side effects. Keep a list of the medicines you take and show it to your healthcare provider and pharmacist.

- Some medicines should not be taken with TAVNEOS.
- Your healthcare provider may prescribe other medicines to treat your disease.

How should I take TAVNEOS?

- Take TAVNEOS exactly as your healthcare provider tells you to take it. Do not stop taking TAVNEOS unless your healthcare provider tells you to.
- Check with your healthcare provider or pharmacist if you are not sure.
- Take 3 capsules of TAVNEOS 2 times daily (morning and evening) with food.
- Your healthcare provider may tell you to take 3 capsules of TAVNEOS 1 time each day if you take certain medicines. Tell your healthcare provider about all the medicines you take.

- Swallow the capsules whole with water. Do not crush, chew or open the capsules.
 - If you miss a dose of TAVNEOS, do not take the missed dose. Just take the next dose at your regular time.
- If you have taken too much TAVNEOS, call your doctor or a Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of TAVNEOS?

TAVNEOS may cause serious side effects, including:

- **See "What is the most important information I should know about TAVNEOS?"**
- **Serious allergic reactions.** TAVNEOS may cause serious allergic reactions. Stop taking TAVNEOS and get emergency medical help right away if you have any of the following signs of a serious allergic reaction:
 - shortness of breath or trouble breathing
 - swollen lips, tongue, throat, or face
 - trouble swallowing
 - chest pain
 - feeling dizzy or faint
 - moderate or severe abdominal pain or vomiting
- **Hepatitis B virus (HBV) reactivation.** Before you take TAVNEOS, your healthcare provider will do blood tests to check for hepatitis B (HBV) infection. If you have had hepatitis B or are a carrier of hepatitis B virus, taking TAVNEOS could cause the virus to become an active infection again. Your healthcare provider may decide to stop TAVNEOS and any other medicines if you have active hepatitis B liver disease. Your healthcare provider will tell you if and when you can start taking TAVNEOS again. Your healthcare provider will monitor you for hepatitis B infection during and for six months after you stop taking TAVNEOS. Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes during treatment with TAVNEOS.
- **Serious infections.** Serious infections can happen in people taking TAVNEOS, and these infections can lead to death. The most common serious infections with TAVNEOS were pneumonia and urinary tract infections. People with serious infections should not take TAVNEOS. Tell your healthcare provider right away if you have any symptoms of infection:
 - fever
 - cold symptoms, such as runny nose or sore throat that do not go away
 - flu symptoms, such as cough, tiredness, and body aches
 - earache or headache
 - pain during urination
 - cold sores in mouth or throat
 - cuts, scrapes, or incisions that are red, warm, swollen, or painful

The most common side effects of TAVNEOS include:

- | | | |
|--------------------------------|----------------------------------|-----------------------|
| • nausea | • headache | |
| • diarrhea | • vomiting | • high blood pressure |
| • tiredness | • stomach pain | • rash |
| • increase in blood creatinine | • burning or prickling sensation | • dizziness |

These are not all the possible side effects of TAVNEOS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TAVNEOS?

Store TAVNEOS capsules at room temperature between 68°F to 77°F (20°C to 25°C).

Keep TAVNEOS and all medicines out of reach of children.

General information about the safe and effective use of TAVNEOS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TAVNEOS for a condition for which it was not prescribed. Do not give TAVNEOS to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information that is written for healthcare professionals.

What are the ingredients in TAVNEOS?

Active ingredient: avacopan

Inactive ingredients: Polyethylene glycol 4000 (PEG-4000), Polyoxyl-40 hydrogenated castor oil.

Manufactured for: ChemoCentryx, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

Patent: <https://pat.amgen.com/tavneos>

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For more information, go to www.TAVNEOS.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 8/2023

PRINCIPAL DISPLAY PANEL - 180 Capsule Bottle Carton

NDC 73556-168-01

TAVNEOS®
(avacopan)
capsules

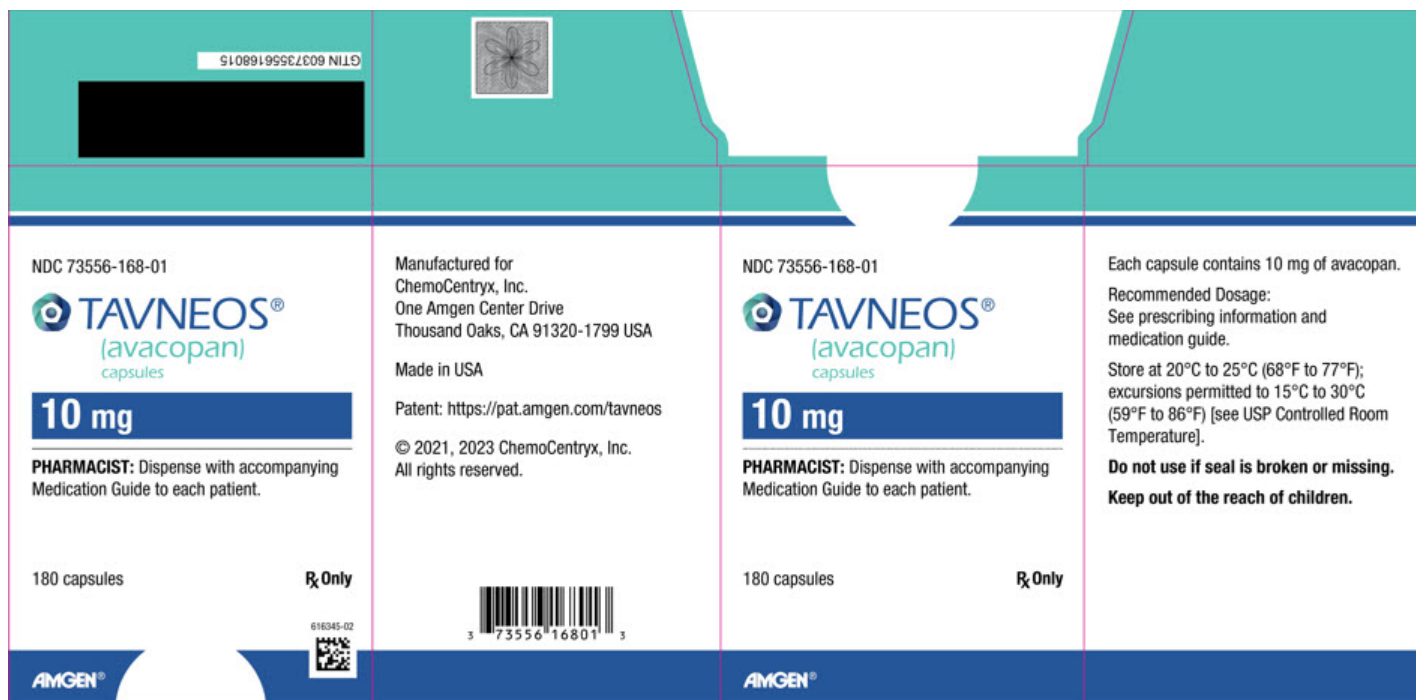
10 mg

PHARMACIST: Dispense with accompanying Medication Guide to each patient.

180 capsules

Rx Only

AMGEN®



PRINCIPAL DISPLAY PANEL - 30 Capsule Bottle Carton

NDC 73556-168-02

TAVNEOS®
(avacopan)
capsules

10 mg

PHARMACIST: Dispense with accompanying
Medication Guide to each patient.

30 capsules
Rx Only

AMGEN®



TAVNEOS

avacopan capsule

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:73556-168 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|-------------------|----------|
| AVACOPAN (UNII: O880NM097T) (AVACOPAN - UNII:O880NM097T) | AVACOPAN | 10 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| POLYOXYL 40 HYDROGENATED CASTOR OIL (UNII: 7YC686GQ8F) | |
| POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95) | |
| FERRIC OXIDE RED (UNII: 1K09F3G675) | |
| FERRIC OXIDE YELLOW (UNII: EX438O2MRT) | |
| TITANIUM DIOXIDE (UNII: 15FIX9V2JP) | |
| GELATIN, UNSPECIFIED (UNII: 2G86QN327L) | |
| FERROSFERRIC OXIDE (UNII: XM0M87F357) | |
| POLYSORBATE 80 (UNII: 6OZP39ZG8H) | |

Product Characteristics

| | | | |
|--------------|---|--------------|----------|
| Color | ORANGE (light orange opaque) , YELLOW (yellow opaque) | Score | no score |
|--------------|---|--------------|----------|

| | | | |
|-----------------|---------|---------------------|--------|
| Shape | CAPSULE | Size | 22mm |
| Flavor | | Imprint Code | CCX168 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|---|----------------------|--------------------|
| 1 | NDC:73556-168-01 | 1 in 1 CARTON | 10/18/2021 | |
| 1 | | 180 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product | | |
| 2 | NDC:73556-168-02 | 1 in 1 CARTON | 10/18/2021 | |
| 2 | | 30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product | | |
| 3 | NDC:73556-168-96 | 1 in 1 CARTON | 10/18/2021 | |
| 3 | | 30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA214487 | 10/18/2021 | |

Labeler - ChemoCentryx, Inc. (002356900)

Revised: 6/2024

ChemoCentryx, Inc.