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PHARMACY / MEDICAL POLICY – 5.01.593

Pharmacologic Treatment of Transthyretin-Mediated Amyloidosis

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Replaces:	N/A

*This policy has been revised. View upcoming changes here.

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Amyloid is an abnormal protein. There are many different reasons why the body makes amyloid. One cause is a change to the TTR gene. This gene provides instructions to the liver about how to make a certain protein. But changes to the TTR gene means this liver protein is faulty. These faulty liver proteins get deposited throughout the body and build up over time. This condition is known as hereditary transthyretin-mediated amyloidosis (hATTR). Symptoms like numbness, pain and weakness in the arms and legs, heart problems, and stomach and bowel problems develop as the condition progresses. One way to treat hATTR is to use certain drugs to reduce the amount of TTR protein the liver makes. This policy describes when these types of drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Amvuttra (vutrisiran) SC
 	
Managed under medical benefit
	Amvuttra (vutrisiran) may be considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) when:
	• The individual is aged 18 years or older
	AND
	• Diagnosis of hereditary transthyretin-mediated amyloidosis is verified by:
	  ○ Documentation of a mutation in the TTR gene
	  OR
	  ○ Tissue biopsy showing amyloid deposition
	AND
	• Presence of symptoms consistent with polyneuropathy of hereditary transthyretin amyloidosis
	  ○ Peripheral sensorimotor polyneuropathy (e.g., tingling or increased pain in the hands or feet, loss of feeling or numbness in the hands or feet, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking)
	  OR
	  ○ Autonomic neuropathy (e.g., postural hypotension, sexual dysfunction, recurrent urinary tract infection)
	AND
	• Polyneuropathy disability (**PND**) score IIIb or less or familial amyloid polyneuropathy (**FAP**) stage 2 or less
	AND
	• Medication is not used in combination with Attruby (acoramidis), Onpattro (patisiran), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), or Wainua (eplontersen)
	AND
	• The individual does not have ANY of the following:
	  ○ New York Heart Association (NYHA) class III or IV heart failure

Drug	Medical Necessity
	○ Sensorimotor or autonomic neuropathy not related to hereditary transthyretin-mediated (hATTR) amyloidosis such as monoclonal gammopathy or an autoimmune disease ○ Prior liver transplantation **AND** • Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticist) **AND** • Dose prescribed is 25 mg injected subcutaneously once every 3 months **Note: Clinical description of PND score** • Score 0 = No symptoms • Score I = Sensory disturbances but preserved walking capability • Score II = Impaired walking capacity but ability to walk without a stick or crutches • Score IIIA = Walking with the help of one stick or crutch • Score IIIB = Walking with the help of two sticks or crutches • Score IV = Confined to a wheelchair or bedridden **Note: Clinical description of FAP stage** • Stage 0 = No symptoms • Stage 1 = Unimpaired ambulation • Stage 2 = Assistance with ambulation required • Stage 3 = Wheelchair-bound or bedridden **Amvuttra (vutrisiran) may be considered medically necessary for the treatment of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) when:** • The individual is aged 18 years or older **AND** • Diagnosis of wild type or hereditary transthyretin-mediated amyloidosis is verified by: ○ Documentation of a mutation in the TTR gene **OR** ○ Tissue biopsy showing amyloid deposition **OR**

Drug	Medical Necessity
	○ Non-biopsy nuclear scintigraphy (**Related Information**) **AND** • Evidence of cardiac involvement as assessed with transthoracic echocardiography, with end diastolic intraventricular septal wall thickness greater than 12 mm **AND** • Clinical history of heart failure with at least one previous hospitalization for heart failure OR clinical evidence of heart failure with volume overload or elevated intracardiac pressures warranting diuretic treatment **AND** • Has a baseline N-terminal pro b-type natriuretic peptide (NT-proBNP) of greater than or equal to 300 pg/mL **AND** • Has New York Heart Association (NYHA) class I-III heart failure with or without evidence of progression **AND** • Does not have any of the following: ○ Presence of light-chain amyloidosis ○ History of liver or heart transplantation ○ Left ventricular assist device **AND** • Completed a 6-minute-walk test (6MWT) of at least 150 meters **AND** • Medication is not used in combination with Attruby (acoramidis), Onpattro (patisiran), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), or Wainua (eplontersen) **AND** • Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticists) **AND** • Dose prescribed is 25 mg injected subcutaneously once every 3 months **Note:** Wild type means the TTR protein is normal, with no documented mutations.

Drug	Medical Necessity
Attruby (acoramidis) oral **Managed under pharmacy benefit**	**Attruby (acoramidis) may be considered medically necessary for the treatment of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) when:** • The individual is aged 18 years or older **AND** • Diagnosis of wild type or hereditary transthyretin-mediated amyloidosis is verified by: ○ Documentation of a mutation in the TTR gene **OR** ○ Tissue biopsy showing amyloid deposition **OR** ○ Non-biopsy nuclear scintigraphy (**Related Information**) **AND** • Evidence of cardiac involvement as assessed with transthoracic echocardiography, with end diastolic intraventricular septal wall thickness greater than 12 mm **AND** • Clinical history of heart failure with at least one previous hospitalization for heart failure OR clinical evidence of heart failure with volume overload or elevated intracardiac pressures warranting diuretic treatment **AND** • Has a baseline N-terminal pro b-type natriuretic peptide (NT-proBNP) of greater than or equal to 300 pg/mL **AND** • Has New York Heart Association (NYHA) class I-III heart failure with or without evidence of progression **AND** • Does not have any of the following: ○ Presence of light-chain amyloidosis ○ History of liver or heart transplantation ○ Left ventricular assist device **AND** • Completed a 6-minute-walk test (6MWT) of at least 150 meters **AND**

Drug	Medical Necessity
	• Medication is not used in combination with Amvuttra (vutrisiran), Onpattro (patisiran), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), or Wainua (eplontersen) **AND** • Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticist) **AND** • Dose prescribed for Attruby (acoramidis) is 712 mg twice daily **Note:** Wild type means the TTR protein is normal, with no documented mutations.
Onpattro (patisiran) IV **Managed under medical benefit**	**Onpattro (patisiran) may be considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) when:** • The individual is aged 18 years or older **AND** • Diagnosis of hereditary transthyretin-mediated amyloidosis is verified by: ○ Documentation of a mutation in the TTR gene **OR** ○ Tissue biopsy showing amyloid deposition **AND** • Presence of symptoms consistent with polyneuropathy of hereditary transthyretin amyloidosis ○ Peripheral sensorimotor polyneuropathy (e.g., tingling or increased pain in the hands or feet, loss of feeling or numbness in the hands or feet, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking) **OR** ○ Autonomic neuropathy (e.g., postural hypotension, sexual dysfunction, recurrent urinary tract infection) **AND** • Polyneuropathy disability (**PND**) score IIIb or less or familial amyloid polyneuropathy (**FAP**) stage 2 or less **AND**

Drug	Medical Necessity

	• Medication is not used in combination with Attruby (acoramidis), Amvuttra (vutrisiran), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), or Wainua (eplontersen)
	AND
	• The individual does not have ANY of the following:
	  ○ New York Heart Association (NYHA) class III or IV heart failure
	  ○ Sensorimotor or autonomic neuropathy not related to hereditary transthyretin-mediated (hATTR) amyloidosis such as monoclonal gammopathy or an autoimmune disease
	  ○ Prior liver transplantation
	AND
	• Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticist)
	AND
	• Dose is based on actual body weight as follows:
	  ○ For individuals weighing less than 100 kg, the dosage is 0.3 mg/kg once every 3 weeks
	  ○ For individuals weighing 100 kg or more, the dosage is 30 mg once every 3 weeks
	
	Note: Clinical description of PND score
	• Score 0 = No symptoms
	• Score I = Sensory disturbances but preserved walking capability
	• Score II = Impaired walking capacity but ability to walk without a stick or crutches
	• Score IIIA = Walking with the help of one stick or crutch
	• Score IIIB = Walking with the help of two sticks or crutches
	• Score IV = Confined to a wheelchair or bedridden
	
	Note: Clinical description of FAP stage
	• Stage 0 = No symptoms
	• Stage 1 = Unimpaired ambulation
	• Stage 2 = Assistance with ambulation required
	• Stage 3 = Wheelchair-bound or bedridden

• **Vyndamax (tafamidis)** • **Vyndaqel (tafamidis meglumine) oral**	**Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine) may be considered medically necessary for the treatment of**

Drug	Medical Necessity

Managed under pharmacy benefit	**cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) when:**
	• The individual is aged 18 years or older
	AND
	• Diagnosis of wild type or hereditary transthyretin-mediated amyloidosis is verified by:
	  ○ Documentation of a mutation in the TTR gene
	  OR
	  ○ Tissue biopsy showing amyloid deposition
	  OR
	  ○ Non-biopsy nuclear scintigraphy (**Related Information**)
	AND
	• Evidence of cardiac involvement as assessed with transthoracic echocardiography, with end diastolic intraventricular septal wall thickness greater than 12 mm
	AND
	• Clinical history of heart failure with at least one previous hospitalization for heart failure OR clinical evidence of heart failure with volume overload or elevated intracardiac pressures warranting diuretic treatment
	AND
	• Has a baseline N-terminal pro b-type natriuretic peptide (NT-proBNP) of greater than or equal to 600 pg/mL
	AND
	• Has New York Heart Association (NYHA) class I-III heart failure with or without evidence of progression
	AND
	• Does not have any of the following:
	  ○ Presence of light-chain amyloidosis
	  ○ History of liver or heart transplantation
	  ○ Left ventricular assist device
	AND
	• Completed a 6-minute-walk test (6MWT) of at least 150 meters
	AND
	• Medication is not used in combination with Attruby (acoramidis), Amvuttra (vutrisiran), Onpattro (patisiran), or Wainua (eplontersen)

Drug	Medical Necessity
	AND • Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticist) **AND** • Dose prescribed for Vyndamax (tafamidis) is 61 mg orally once daily **OR** • Dose prescribed for Vyndaqel (tafamidis meglumine) is 80 mg orally once daily **Note:** Wild type means the TTR protein is normal, with no documented mutations.
Wainua (eplontersen) SC **Managed under pharmacy and medical benefit**	**Wainua (eplontersen) may be considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) when:** • The individual is aged 18 years or older **AND** • Diagnosis of hereditary transthyretin-mediated amyloidosis is verified by: ○ Documentation of a mutation in the TTR gene **OR** ○ Tissue biopsy showing amyloid deposition **AND** • Presence of symptoms consistent with polyneuropathy of hereditary transthyretin amyloidosis ○ Peripheral sensorimotor polyneuropathy (e.g., tingling or increased pain in the hands or feet, loss of feeling or numbness in the hands or feet, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking) **OR** ○ Autonomic neuropathy (e.g., postural hypotension, sexual dysfunction, recurrent urinary tract infection) **AND** • Polyneuropathy disability (**PND**) score IIIb or less or familial amyloid polyneuropathy (**FAP**) stage 2 or less

Drug	Medical Necessity

	AND
	• Medication is not used in combination with Attruby (acoramidis), Amvuttra (vutrisiran), Onpattro (patisiran), Vyndamax (tafamidis), or Vyndaqel (tafamidis meglumine)
	AND
	• The individual does not have ANY of the following:
	  ○ New York Heart Association (NYHA) class III or IV heart failure
	  ○ Sensorimotor or autonomic neuropathy not related to hereditary transthyretin-mediated (hATTR) amyloidosis such as monoclonal gammopathy or an autoimmune disease
	  ○ Prior liver transplantation
	AND
	• Medication is prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticist)
	AND
	• Dose prescribed is 45 mg injected subcutaneously every 4 weeks
	
	Note: Clinical description of PND score
	• Score 0 = No symptoms
	• Score I = Sensory disturbances but preserved walking capability
	• Score II = Impaired walking capacity but ability to walk without a stick or crutches
	• Score IIIA = Walking with the help of one stick or crutch
	• Score IIIB = Walking with the help of two sticks or crutches
	• Score IV = Confined to a wheelchair or bedridden
	
	Note: Clinical description of FAP stage
	• Stage 0 = No symptoms
	• Stage 1 = Unimpaired ambulation
	• Stage 2 = Assistance with ambulation required
	• Stage 3 = Wheelchair-bound or bedridden

Drug	Investigational
• **Amvuttra (vutrisiran)** • **Attruby (acoramidis)** • **Onpattro (patisiran)**	**All other uses of Amvuttra (vutrisiran), Attruby (acoramidis), Onpattro (patisiran), Vyndamax (tafamidis), Vyndaqel**

Drug	Investigational
• **Vyndamax (tafamidis)** • **Vyndaqel (tafamidis meglumine)** • **Wainua (eplontersen)**	**(tafamidis meglumine), and Wainua (eplontersen) for conditions not outlined in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Approval	Criteria
Initial authorization	**All drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria for Amvuttra, Onpattro, and Wainua for the treatment of hATTR	**Amvuttra, Onpattro, or Wainua may be approved for periods of 12 months if the above drug specific criteria are met and the individual has shown and continues to show:** • Efficacy documented in the medical record indicating positive clinical response (e.g., improved or stable motor, neurologic, cardiac function, or serum TTR levels) **AND** • Improvement or stability in one of the following from baseline: PND score or FAP stage **AND** • Absence of treatment limiting toxicity
Re-authorization criteria for Amvuttra, Attruby, Vyndamax, and Vyndaqel for the treatment of ATTR-CM	**Amvuttra, Attruby, Vyndamax, or Vyndaqel may be approved for periods of 12 months if the above Amvuttra, Attruby, Vyndamax, and Vyndaqel criteria are met and the individual has shown and continues to show efficacy documented in the medical record indicating positive clinical response (e.g., 6-Minute Walk Test [6MWT], Kansas City Cardiomyopathy Questionnaire-Overall Summary [KCCQ-OS] score).**

Documentation Requirements
For Amvuttra, Onpattro, or Wainua for the treatment of hATTR the individual's medical records submitted for review should document that medical necessity criteria are met. The records should include the following: • Office visit notes that contain the relevant history and physical evaluation information **AND**

Documentation Requirements

- Documented TTR mutation OR tissue biopsy showing amyloid deposition

AND

- Results of the PND score or FAP stage

AND

- Dose and frequency of prescribed medication

For Amvuttra, Attruby, Vyndamax, or Vyndaqel for the treatment of ATTR-CM the individual's medical records submitted for review should document that medical necessity criteria are met. The records should include the following:

- Office visit notes that contain the relevant history and physical evaluation information

Coding

Code	Description
HCPCS	
C9399	Unclassified drugs or biologicals (used to report: Wainua)
J0222	Injection, patisiran (Onpattro), 0.1 mg
J0225	Injection, vutrisiran (Amvuttra), 1 mg
J3490	Unclassified drugs (use to report: Wainua)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Benefit Application

Pharmacy Benefit

Attruby (acoramidis), Vyndaqel (tafamidis meglumine), and Vyndamax (tafamidis) are managed through the pharmacy benefit.

Medical Benefit

Onpattro (patisiran) and Amvuttra (vutrisiran) are managed through the medical benefit.

Medical and Pharmacy Benefit

Wainua (eplontersen) is managed through both the pharmacy and medical benefit.

Bone Scintigraphy

The use of ^{99m}Tc bone-avid compounds for bone scintigraphy allows for noninvasive diagnosis of ATTR-CM. ^{99m}Tc compounds include PYP (pyrophosphate), 3,3-diphosphono-1,2-propanodicarboxylic acid, and hydromethylene diphosphonate, and PYP is used in the United States. In the absence of a light-chain abnormality, the ^{99m}Tc-PYP scan is diagnostic of ATTR-CM if there is grade 2/3 cardiac uptake or an H/CL ratio of >1.5. In fact, the presence of grade 2/3 cardiac uptake in the absence of a monoclonal protein in serum or urine has a very high specificity and positive predictive value for ATTR-CM.

Evidence Review

Description

Hereditary transthyretin amyloidosis (hATTR), formerly known as familial amyloidotic polyneuropathy (FAP), is a rare, progressive disorder characterized by the extracellular deposition of TTR protein. hATTR can affect multiple organs and body systems, such as the

heart, nervous system, gastrointestinal (GI) tract, and kidney. Symptoms may include autonomic dysfunction, GI dysfunction, ocular manifestation, cardiac manifestation, compromised renal function, or carpal tunnel syndrome. The most common mutation associated with hATTR is Val30Met. Although some mutations are associated mainly with polyneuropathy or cardiomyopathy, most individuals have mixed clinical phenotypes. If untreated, death occurs about 10 years after onset of hATTR.

The disease course begins with unimpaired ambulation (FAP stage 1), then requiring ambulation (FAP stage 2), which proceeds to wheelchair confinement (FAP stage 3), where individuals experience life-impacting symptoms including burning neuropathic pain, loss of sensation in hands and feet, diarrhea/constipation, sexual impotence, and dizziness/fainting. The median survival for individuals with hATTR with polyneuropathy is reported as 5-15 years.

hATTR affects at least 10,000 people worldwide with about >120 TTR mutations being reported, with about 3,000-5,000 people in the U.S. However, symptoms of hATTR do not always start in one specific organ and the disease is often masked. As a result, these numbers may be underestimated due to under-diagnosis. Quantifying the disease burden in hATTR remains challenging since there is no single test that captures all the symptoms of the condition. Tests demonstrated that both mental and physical health in individuals with hATTR were substantially lower than an age-match controlled group of individuals not receiving treatment.

The protein TTR is synthesized and secreted by the liver, where it transports thyroxine and retinol. Mutations in TTR destabilize the protein, causing misfolding into a beta-pleated sheet configuration and forming insoluble amyloid fibrils. This mutation results in an autosomal dominant disorder primarily affecting the nerves and heart. With different mutations, symptomatic manifestations may vary even among family members.

Diagnosis

Diagnosis of hATTR based on clinical signs and symptoms is difficult because of heterogeneity in clinical manifestations and the nonspecific nature of signs and symptoms that may mimic other conditions. Furthermore, the age of onset and rate of progression are highly variable from patient to patient. As a result, many patients are misdiagnosed or their diagnosis is delayed, and patients often see physicians across multiple specialties before receiving an accurate diagnosis.

To confirm the diagnosis, proven amyloid deposition in biopsy specimens and identification of a pathogenic variant in the transthyretin gene are necessary. Amyloid deposition in the biopsied tissues can be confirmed by using Congo red staining and, ideally, immunohistochemical study as well as laser capture tandem mass spectrometry. However, mass spectrometry can only

demonstrate a mass difference between wild-type and transthyretin protein variants in serum. It does not specify the site and kind of amino acid substitution in a number of disease-related transthyretin variants; thus, DNA sequencing is usually required. Sequence analysis of the transthyretin gene, the only gene in which mutation is known to cause hATTR, detects more than 99% of pathogenic variants.

Summary of Evidence

Amvuttra (vutrisiran)

Vutrisiran was studied in a multicenter, open-label, randomized, Phase 3 study, HELIOS-A.1 The trial included 164 individuals with 122 randomized to vutrisiran and 42 to patisiran. Inclusion criteria were ages 18-85 years, hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), Karnofsky performance status (KPS) ≥60%, polyneuropathy disability (PND) ≤IIIb, and Neuropathy Impairment Scale (NIS) 5-130 out of 244 (higher scores indicate greater disability). Exclusion criteria included individuals undergoing liver transplantation and those with New York Heart Association (NYHA) class III or IV heart failure (HF). Individuals were randomized to vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV q3 weeks for 18 months. The primary endpoint was change from baseline in Modified Neuropathy Impairment Scale +7 (mNIS+7) at Month 9. Of note, most comparisons including the primary endpoint compared the vutrisiran group to the placebo arm of the APOLLO trial. The APOLLO trial was a randomized, double-blind, placebo-controlled trial which randomized 225 individuals with hATTR-PN to patisiran or placebo for 18 months. While the inclusion criteria were similar in both trials, several baseline characteristics differed between HELIOS-A individuals and the APOLLO placebo group including mNIS+7, Norfolk quality of life in diabetic neuropathy (QoL-DN), and ten meter walk test (10-MWT). At Month 9, the least square (LS) mean change in mNIS+7 score was significantly less with vutrisiran (indicating less disability) than with the APOLLO placebo group (-2.24 vs 14.76). Of note, this difference was reported to be statistically significant; however, the p-value was not provided. At 18 months, the difference in LS mean change in mNIS+7 remained significant for vutrisiran (-0.46 vutrisiran vs 28.1 APOLLO placebo, p=6.50 x10-20). Additionally, all other secondary outcomes also significantly favored vutrisiran (Norfolk QOL-DN, 10-MWT, modified body mass index [mBMI], and Rasch-built Overall Disability Scale [R-ODS]). Vutrisiran was compared to the HELIOS-A patisiran group for the secondary outcome of mean steady state transthyretin (TTR) reduction from baseline; vutrisiran was noninferior to patisiran at 18 months (median TTR difference 5.28%, 95% CI 1.17-9.25, lower limit of CI >-10%).

Common adverse events occurring in >10% of individuals were falls, pain in extremity, diarrhea, peripheral edema, urinary tract infection (UTI), arthralgia, dizziness. Arthralgia and pain in extremity occurred more frequently with vutrisiran than APOLLO placebo. Injection-site reactions occurred in 4.1% of individuals on vutrisiran. Serious AEs (SAEs) and severe AEs occurred numerically less frequently with vutrisiran than APOLLO placebo or patisiran (SAEs: 26% vutrisiran, 40% APOLLO placebo, 43% patisiran; severe AEs: 16%, 36%, 38%, respectively). Two SAEs (dyslipidemia and UTI) were considered related to vutrisiran. No hepatic, hematologic, or renal safety signals were considered related to vutrisiran. No discontinuations due to AEs were considered related to vutrisiran.

Vutrisiran was evaluated in the Phase 3 HELIOS-B trial (NCT04153149), which included 654 adult patients with wild-type or hereditary ATTR-CM who were randomized to receive vutrisiran or placebo. Patients were permitted to be taking a tafamidis product at baseline or initiate tafamidis during the double-blind period. Treatment assignment was stratified by baseline tafamidis use (yes versus no), ATTR disease type (wtATTR or hATTR amyloidosis), and by baseline New York Heart Association (NYHA) Class I or II and age <75 years versus all other. At baseline, 40% of patients were on tafamidis. The mean age of study participants was 75 years, 93% were male, 84% were White, 7% were Black or African American, 6% were Asian, 2% did not report race and 1% were race other, 88% had wildtype ATTR, 13% were NYHA Class I, 78% were NYHA Class II, and 9% NYHA Class III. No significant imbalance in baseline characteristics was observed between the two treatment groups.

The primary efficacy endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure [UHF] visits) during the double-blind treatment period of up to 36 months, evaluated in the overall population and in the monotherapy population (defined as patients not receiving tafamidis at study baseline). Vutrisiran led to significant reduction in the risk of all-cause mortality and recurrent CV events compared to placebo; in the overall and monotherapy populations, the risk was reduced by 28% and 33%, respectively. The majority of deaths (77%) were CV-related. Both components of the primary composite endpoint individually contributed to the treatment effect in the overall and monotherapy populations.

The treatment effects of vutrisiran on functional capacity and health status were assessed by the change from baseline to Month 30 in distance walked on the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively. At Month 30, the least-squares (LS) mean difference in change from baseline in distance walked on the 6MWT was 22 meters (95% CI: 8, 35; P = 0.002) and 25 meters (95% CI: 7, 44; P = 0.006) favoring vutrisiran over placebo in the overall population and monotherapy population, respectively. At Month 30, the LS mean difference in the change from baseline on the KCCQ-OS

score was 6 (95% CI: 2, 9; *P* = 0.001) and 8 (95% CI: 4, 13; *P* = 0.0003) favoring vutrisiran over placebo in the overall population and monotherapy population, respectively.

In HELIOS-B, safety was evaluated among 654 patients with ATTR-CM, which included 257 patients treated with vutrisiran for ≥30 months and 77 patients treated with vutrisiran for ≥36 months. No new safety issues were identified. Vutrisiran can cause reduced serum vitamin A levels. Therefore, patients should supplement with the recommended daily allowance of vitamin A, and providers should refer patients to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. In the HELIOS-B trial, 82% of patients treated with vutrisiran had normal vitamin A levels at baseline, and 80% of those with a normal baseline developed low vitamin A levels.

Attruby (acoramidis)

Acoramidis is a selective stabilizer of transthyretin (TTR) that was evaluated in a multicenter, international, randomized, double-blind, placebo-controlled study in 611 adult individuals with wild-type or variant (hereditary or de novo) ATTR-CM. Participants were randomized (2:1) to receive acoramidis 712 mg (n=409) or placebo (n=202) twice daily for 30 months. The treatment assignment was stratified by type of ATTR-CM [variant (ATTRv-CM) or wild-type (ATTRwt-CM)], NT-proBNP level, and estimated glomerular filtration rate (eGFR). The mean age of study participants was 77 years, 90.8% were male, 87.9% were White, 4.7% Black or African American, 2.1% Asian, 5.3% race other, 19% had a history of permanent pacemaker and 58% had a history of atrial fibrillation.

Participants were permitted to initiate open-label tafamidis after 12 months in the study. A total of 107 participants received tafamidis: 61 (14.9%) in the acoramidis arm and 46 (22.8%) in the placebo arm. The median time to initiation of tafamidis for these 107 participants was 17 months.

The primary composite endpoint included all-cause mortality (ACM) and cumulative frequency of cardiovascular-related hospitalizations (CVH) over 30 months, analyzed hierarchically using the stratified Finkelstein-Schoenfeld (F-S) test. The F-S test demonstrated a statistically significant reduction (p=0.018) in ACM and cumulative frequency of CVH in the acoramidis arm versus the placebo arm. All-cause mortality was reported in 19% and 26% of participants in the acoramidis and placebo groups, respectively. The majority (79%) of the deaths were cardiovascular. CVH was reported in 27% and 43% of participants in the acoramidis and placebo groups, respectively. The mean number of CVH events was 0.3 vs 0.6 per year. The majority

(59%) of CVH were heart failure hospitalizations reported in 13% and 26% of the participants in the acoramidis and placebo groups, respectively.

Onpattro (patisiran)

Fair quality evidence from the Phase 2 and APOLLO studies showed that patisiran 0.3 mg/kg intravenously (IV) every three weeks (Q3W) is effective in reducing transthyretin (TTR levels) and improving their modified neuropathy impairment scale+7 (mNIS+7) score, respectively, in adults diagnosed with hereditary transthyretin amyloidosis (hATTR) and neuropathy. The 0.3 mg/kg IV Q3W dosing regimen demonstrated the highest maximum TTR knockdown (KD) and TTR KD at nadir for both dose 1 (94.2% and 83.8%) and dose 2 (96.0% and 86.7%) compared to other dosing regimens (0.01, 0.05,0.15, and 0.3 mg/kg every four weeks [Q4W]). Patisiran showed significant improvement in individuals' change in mNIS+7 scores from baseline compared to placebo (-6.03 vs. 27.96), suggesting improvement in autonomic function. This is further proven in the Phase 2 open-label extension (OLE) trial, where individuals were on patisiran for 24 months and had a change in mNIS+7 from baseline of -7.0. Secondary endpoints in the APOLLO trial saw improved scores as well, most notably in assessing quality of life using the Norfolk quality of life-diabetic neuropathy (QoL-DN) scale (-6.7 vs. 14.4).

Mild to moderate adverse events (AEs) were common in patisiran. Most AEs were infused-related reactions (IRRs), which occurred in 10.3% of individuals in the Phase 2 trial and 18.9% of subjects in the patisiran group from the APOLLO trial. The Phase 2 OLE trial demonstrated similar results as well with 22.2% of subjects experiencing IRRs. Researchers attempted to prevent IRRs by pre-medicating individuals with dexamethasone, acetaminophen, an H1 blocker, and an H2 blocker. As a result, pill burden may play a role in adherence and managing AEs. Another common AE was peripheral edema (29.7% in patisiran vs. 22.1% in placebo) which decreased over time with no individual needing to discontinue treatment. The Phase 2 trial reported one individual experiencing a urinary tract infection (UTI), sepsis, nausea, and vomiting. Another individual reported cellulitis, nausea, and vomiting. Because one individual experienced these symptoms, it is difficult to associate patisiran with these serious adverse events (SAEs). The APOLLO study had 36.5% of the patisiran group experience a SAE. The most common SAE found was diarrhea in 5.4% of individuals. No increase in observed frequency of events for patisiran compared to placebo group by SOC.

Vyndamax and Vyndaqel

Tafamidis was studied in a large, multicenter, placebo-controlled, double-blind, 30-month, Phase 3 trial (ATTR-ACT trial) which randomized 441 individuals with transthyretin amyloid cardiomyopathy (AATR-CM) to tafamidis 80 mg/day, tafamidis 20 mg/day, or placebo. The study included adults up to 90 years of age with confirmed amyloid transthyretin wild type (ATTRwt) or amyloid transthyretin due to a mutation (ATTRm) with amyloid cardiac involvement and heart failure (HF). The primary outcome measures were all-cause mortality and CV-related hospitalization which were assessed hierarchically. The study used the Finkelstein-Schoenfeld method to assess statistical significance. This method pairs each individual in a given strata with every other individual in that strata, assigning a +1 to the better individual and -1 to the worse individual based on all-cause mortality followed by cardiovascular (CV)-related hospitalization if both individuals remain alive. These values are summed to create the test statistic. According to the Finkelstein-Schoenfeld method, pooled tafamidis was superior to placebo over 30 months ($p<0.001$) with a win ratio of 1.695 (95% CI 1.255-2.289). All-cause mortality was significantly decreased with pooled tafamidis compared to placebo with a 30% risk reduction (HR 0.7, 95% CI 0.51-0.96). The risk of CV-related hospitalization significantly decreased with pooled tafamidis compared to placebo (RR 0.68, 95% CI 0.56-0.81). The least squares (LS) mean change from baseline to month 30 in the 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire – overall summary (KCCQ-OS) both significantly favored pooled tafamidis (6MWT: -55 vs -131 tafamidis vs placebo, $p<0.001$; KCCQ-OS -7 vs -21 respectively, $p<0.001$). All assessments met criteria for clinical as well as statistical significance. Subgroup assessment found results favored tafamidis in all-cause mortality and CV-hospitalization except for CV-related hospitalization in New York Heart Association (NYHA) Class III individuals which significantly favored placebo. Of note, no difference in all-cause mortality was seen with the 20 mg dose of tafamidis compared to the 80 mg dose (26.1% vs 27.8%, respectively, statistical analysis not performed).

The prescribing information for tafamidis describes adverse events (AEs) seen with tafamidis as equivalent to placebo. In the ATTR-ACT trial, none of the AEs seen with tafamidis occurred with an incidence ≥4% greater than the incidence seen with placebo. There are no contraindications or warnings. According to the prescribing information, in the 30-month placebo-controlled study, discontinuation due to AEs occurred in 7% of individuals on Vyndaqel 80 mg, 6% on Vyndaqel 20 mg, and 6% on placebo. Of note, the published ATTR-ACT trial lists discontinuation rates due to treatment-emergent AEs (TEAEs) as 21.2% with tafamidis and 28.8% with placebo and temporary discontinuation due to TEAE as 20.1% and 26%, respectively.

Wainua

Wainua is a TTR–directed antisense oligonucleotide (ASO). Wainua is indicated for the treatment of adults with hATTR-PN. Wainua is self-administered. The efficacy and safety of Wainua were studied in the Phase 3, randomized, open-label, multicenter NEURO-TTRansform trial in individuals with hATTR-PN. The approval of Wainua was based on results from the 35-week interim analysis of data from the Phase 3 NEURO-TTRansform trial, which showed treatment with Wainua significantly lowered serum transthyretin (TTR) concentration, lessened neuropathic impairment, and improved quality of life compared with placebo.

Regulatory Status

In August 2018, patisiran (Onpattro, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

In June 2022, vutrisiran (Amvuttra, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults and in March 2025 it was approved for the treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits.

In December 2023, eplontersen (Wainua, AstraZeneca Pharmaceuticals, LP) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

In May 2019, Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) were approved by the FDA for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

In November 2024, acoramidis (Attruby, BridgeBio Pharma, Inc) was approved by the FDA for the treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular death and cardiovascular-related hospitalization.

2020 Update

A literature search from 12/1/2019 through 6/30/2020 did not identify new information requiring change to the medical policy criteria.

2021 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search on the management of the polyneuropathy and cardiomyopathy of hereditary transthyretin-mediated amyloidosis. No new information was identified that would require changes to the medical policy criteria.

2022 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search on the management of transthyretin-mediated amyloidosis. No new information was identified that would require changes to the medical policy criteria.

2023 Update

Reviewed World Heart Federation Consensus on Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM) guideline and conducted a literature search on management of transthyretin-mediated amyloidosis from 10/31/2022 through 11/1/2023. No new evidence was identified that would require changes to the medical policy criteria.

2024 Update

Added coverage criteria for Wainua (eplontersen) for the treatment of certain adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis. Added requirement that Wainua (eplontersen) may not be used in combination with Amvuttra, Onpattro, or Tegsedi. Updated Amvuttra (vutrisiran), Onpattro (patisiran), and Tegsedi (inotersen) coverage criteria to allow confirmation of diagnosis by tissue biopsy or genetic testing as well as ensure the individual does not have any of the following: NYHA class III or IV heart failure, sensorimotor or autonomic neuropathy not related to hereditary transthyretin-mediated amyloidosis, or a prior liver transplantation. Updated Vyndamax/Vyndaqel (tafamidis) coverage criteria to allow confirmation of diagnosis by tissue biopsy or genetic testing, ensure the individual has end-diastolic interventricular septal wall thickness exceeding 12 mm on echocardiography, a history of heart failure, baseline NT-proBNP of ≥ 600 pg/mL, and does not have any of the following:

NYHA class IV heart failure, presence of light-chain amyloidosis, history of heart or liver transplantation, or an implanted cardiac device. Updated all coverage criteria to remove genetic testing for confirmation of diagnosis and replaced it with PYP scintigraphy. Updated Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine) coverage criteria to include quantity limits. Removed Tegesdi (inotersen) from the medical policy.

2025 Update

Added coverage criteria for Attruby (acoramidis) for the treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults. Updated coverage criteria for Amvuttra, Onpattro, and Wainua for the diagnosis of ATTR-CM. Updated Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine) coverage criteria for the diagnosis of ATTR-CM, removed NYHA class IV heart failure as exclusion, updated the assessment of cardiac involvement and history of heart failure, added inclusion of a 6-minute walk test (6MWT) requirement, and added quantity limits. Removed Tegsedi (inotersen) from the medical policy as the product has been with withdrawn from the market by the manufacturer Akcea Therapeutics, Inc. Per the manufacturer, Tegsedi was discontinued on September 27, 2024, due to low utilization and the decision was not related to manufacturing, quality, or safety matters. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

2026 Update

Updated the coverage criteria for Amvuttra (vutrisiran), Onpattro (patisiran), and Wainua (eplontersen) for the treatment of hATTR to require documentation of a mutation in the TTR gene or tissue biopsy showing amyloid deposition and removed requirement to have two confirmatory diagnostic tests. Updated the coverage criteria for Amvuttra, Attruby (acoramidis), Vyndamax (tafamidis), and Vyndaqel (tafamidis meglumine) for the treatment of ATTR-CM to require documentation of a mutation in the TTR gene, tissue biopsy showing amyloid deposition, or non-biopsy nuclear scintigraphy and removed requirement to have two confirmatory diagnostic tests. For Amvuttra, Attruby, Vyndamax, and Vyndaqel for the treatment of ATTR-CM changed does not have an implanted cardiac device to does not have a left ventricular assist device and added a note to clarify that wild type means the TTR protein is normal, with no documented mutations. Updated coverage criteria for all medications to allow for medications to be prescribed by or in consultation with physicians experienced in the

treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticists). Added to Evidence Review information on the diagnosis of hATTR and the regulatory status for all medications in the policy.

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History

Date	Comments
04/01/19	New policy, approved March 12, 2019. Add to Prescription Drug section. Onpattro (patisiran) and Tegsedi (inotersen) may be considered medically necessary when criteria are met. They are considered investigational for all other uses.
10/01/19	Coding update, added HCPCS code J0222 (new code effective 10/1/19).
12/01/19	Interim Review, approved November 12, 2019. Added coverage criteria for Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine).
11/01/20	Annual Review, approved October 22, 2020. No change to policy statements. Removed HCPCS J3490.
01/01/22	Annual Review, approved December 2, 2021. No changes to policy statements.
06/01/22	Annual Review, approved May 9, 2022. No changes to policy statements.
08/01/22	Interim Review, approved July 12, 2022. Added coverage criteria for Amvuttra (vutrisiran) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Updated criteria for Onpattro, Tegsedi, Vyndamax, and Vyndaqel documenting these drugs are not to be used in combination with Amvuttra.
01/01/23	Coding update. Added new HCPC code J0225 for Amvuttra™. Removed Amvuttra™ from HCPC code J3590.
02/01/23	Interim Review, approved January 10, 2023. Removed from Amvuttra the requirement to try and fail Onpattro or Tegsedi first. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/23	Annual Review, approved November 20, 2023. No changes to policy statements. Removed HCPCS code J3590 and added J3490 to report Tegsedi.
03/01/24	Annual Review, approved February 13, 2024. Added coverage criteria for Wainua (eplontersen) for the treatment of certain adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis. Added requirement that Wainua (eplontersen) may not be used in combination with Amvuttra, Onpattro, or Tegsedi. Updated Amvuttra (vutrisiran), Onpattro (patisiran), and Tegsedi (inotersen) coverage criteria to allow confirmation of diagnosis by tissue biopsy or genetic testing as well as ensure the individual does not have any of the following: NYHA class III or IV heart failure, sensorimotor or autonomic neuropathy not related to hereditary transthyretin-mediated amyloidosis, or a prior liver transplantation. Updated Vyndamax/Vyndaqel (tafamidis) coverage criteria to allow confirmation of diagnosis by tissue biopsy or genetic testing, ensure the individual has end-diastolic interventricular septal wall thickness exceeding 12 mm on echocardiography, a history of heart failure, baseline NT-proBNP of ≥ 600 pg/mL, and does not have any of the following: NYHA class IV

Date	Comments
	heart failure, presence of light-chain amyloidosis, history of heart or liver transplantation, or an implanted cardiac device.
02/01/25	Annual Review, approved January 14, 2025. Added coverage criteria for Attruby (acoramidis) for the treatment of ATTR-CM. Updated coverage criteria for Amvuttra, Onpattro, and Wainua for the diagnosis of ATTR-CM. Updated Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine) coverage criteria for the diagnosis of ATTR-CM, removed NYHA class IV heart failure as exclusion, updated the assessment of cardiac involvement and history of heart failure, added inclusion of a 6MWT requirement and added quantity limits. Removed the drug Tegesdi (inotersen) from the medical policy as the product has been with withdrawn from the market by the manufacturer. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated policy criteria for Amvuttra, Onpattro, and Wainua are effective May 6, 2025, following a 90-day provider notification. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Removed drug name Tegesdi from unlisted HCPCS code, J3490.
04/01/25	Interim Review, approved March 24, 2025. Minor correction made to heart failure requirements for Attruby (acoramidis), Vyndaqel (tafamidis meglumine), and Vyndamax (tafamidis).
07/01/25	Interim Review, approved June 10, 2025. Added a new indication to Amvuttra (vutrisiran) for the treatment of ATTR-CM.
04/01/26	Annual Review, approved March 10, 2026. Updated the coverage criteria for Amvuttra (vutrisiran), Onpattro (patisiran), and Wainua (eplontersen) for the treatment of hATTR to require documentation of a mutation in the TTR gene or tissue biopsy showing amyloid deposition and removed requirement to have two confirmatory diagnostic tests. Updated the coverage criteria for Amvuttra, Attruby (acoramidis), Vyndamax (tafamidis), and Vyndaqel (tafamidis meglumine) for the treatment of ATTR-CM to require documentation of a mutation in the TTR gene, tissue biopsy showing amyloid deposition, or non-biopsy nuclear scintigraphy and removed requirement to have two confirmatory diagnostic tests. For Amvuttra, Attruby, Vyndamax, and Vyndaqel for the treatment of ATTR-CM changed does not have an implanted cardiac device to does not have a left ventricular assist device and added a note to clarify that wild type means the TTR protein is normal, with no documented mutations. Updated coverage criteria for all medications to allow for medications to be prescribed by or in consultation with physicians experienced in the treatment of ATTR amyloidosis (e.g., neurologist, cardiologist, geneticists).

and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.