Medical Policy Bulletin

Title:
Patisiran (Onpattro™) and vutrisiran (Amvuttra™)
Policy #:
MA08.100e

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

INITIAL THERAPY
Wild-Type or Hereditary Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

Vutrisiran (Amvuttra) is considered medically necessary and, therefore, covered for individuals 18 years of age or older with ATTR-CM when all of the following criteria, including dosing and frequency requirements listed below, are met:

- The individual has a diagnosis of wild-type ATTR-CM (no genetic variation) or hereditary ATTR-CM (pathogenic variation(s) in the transthyretin [TTR] gene [e.g., variation of Val122Ile]) confirmed by ONE of the following:
  - presence of TTR amyloid deposits in a tissue-biopsy specimen
  - fulfillment of validated scintigraphy-based diagnostic criteria for ATTR-CM, in the absence of light-chain amyloidosis
- The individual has evidence of cardiac involvement by transthoracic echocardiography, with an end-diastolic interventricular septal wall thickness exceeding 12 mm
- The individual has ONE of the following features of heart failure:
  - History of heart failure, with at least one previous hospitalization for heart failure
  - Clinical evidence of heart failure (i.e., signs and symptoms of volume overload [e.g., dyspnea, edema] or elevated intracardiac pressures warranting diuretic treatment)
- The individual has documentation of New York Heart Association (NYHA) Functional Class I, II, or III heart failure

- Prescribed by or in consultation with a cardiologist, or professional provider specializing in the treatment of amyloidosis

Polyneuropathy of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Patisiran (Onpattro) or vutrisiran (Amvuttra) are considered medically necessary and, therefore, covered for individuals 18 years of age or older with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy when all of the following criteria, including dosing and frequency requirements listed below, are met:

- Diagnosis of hATTR amyloidosis with polyneuropathy is confirmed by molecular genetic testing that reveals pathogenic variation(s) in the transthyretin (TTR) gene (e.g., variation of V30M, which is the most common pathogenic variant consisting of a point mutation)
- Documentation of one of the following baseline ambulation parameters in either the Familial Amyloid Polyneuropathy (FAP) stage or Polyneuropathy Disability (PND) Score (see Guidelines Section for description of scores):
    - Stage 1 (unimpaired ambulation) or 2 (assisted ambulation) on the FAP staging tool
    - Score 0, I, II, IIIa, or IIIb on the PND scoring tool
- Documented presence of cardiac or renal manifestations, or motor, sensory, or autonomic neuropathy related to the hATTR amyloidosis with polyneuropathy (e.g., neuropathic pain, muscle weakness that affects daily living, orthostatic hypotension, diarrhea, nausea, vomiting, heart failure, arrhythmias, proteinuria, renal failure; vision disorders, such as vitreous opacity, dry eyes, glaucoma, or pupils with an irregular or scalloped appearance)
- Prescribed by or in consultation with a neurologist, geneticist, or professional provider specializing in the treatment of amyloidosis
- Individual has not had a liver transplant or is unlikely to be a candidate
- Patisiran (Onpattro) or vutrisiran (Amvuttra) will not be used in combination with each other, any other RNA interference agents (e.g., eplontersen [Wainua], inotersen [Tegsedi]), or transthyretin stabilizers (e.g., acoramidis [Attruby], tafamidis [Vyndaqel, Vyndamax])

CONTINUATION THERAPY

Wild-Type or Hereditary Transthyretin amyloidosis with cardiomyopathy (ATTR-CM)

Vutrisiran (Amvuttra) is considered medically necessary and, therefore, covered for continuation therapy for the treatment of ATTR-CM when the individual meets both of the following criteria:

- Documented improvement or stability of ATTR-CM (e.g., reduction in CV-related hospitalizations or urgent visits, reduction in serum cardiac biomarkers [B-type natriuretic peptide, cardiac troponin])
- The individual does not have New York Heart Association (NYHA) Functional Class IV heart failure

Polyneuropathy of Hereditary Transthyretin-mediated (hATTR) amyloidosis

Patisiran (Onpattro) or vutrisiran (Amvuttra) are considered medically necessary and, therefore, covered for continuation therapy following at least 18 months of therapy for the treatment of hATTR amyloidosis with polyneuropathy when the individual meets both of the following criteria:

- Recent documentation of one of the following ambulation parameters (see Guidelines Section for description of scores):
    - Stage 1 (unimpaired ambulation) or 2 (assisted ambulation) on the FAP staging tool
    - Score 0, I, II, IIIa, or IIIb on the PND scoring tool
- Documented improvement or stability in the signs and symptoms of hATTR amyloidosis with polyneuropathy (e.g., neuropathic pain, muscle weakness that affects daily living, orthostatic hypotension, diarrhea, nausea, vomiting, heart failure, arrhythmias, proteinuria, renal failure; vision disorders, such as vitreous opacity, dry eyes, glaucoma, or pupils with an irregular or scalloped appearance), based on objective or standard evaluation scales

NOTE:

Evio has been selected by the Company to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies. Patisiran (Onpattro) and vutrisiran (Amvuttra) are included in the portfolio of high-cost drug therapies for which Evio will be tracking clinical outcomes. If a patient meets all medical policy provisions and is approved to receive treatment, the requesting professional provider or member must attest and agree to providing clinical outcomes data and information via Evio's secure web portal as requested.

DOSING AND FREQUENCY REQUIREMENTS

PATISIRAN (ONPATTRO)
The following dosage and frequency information was taken from the prescribing information for this product:

- Individuals weighing less than 100 kg: 0.3 mg/kg once every 3 weeks via intravenous infusion
- Individuals weighing 100 kg or more: 30 mg once every 3 weeks via intravenous infusion

VUTRISIRAN (AMVUTTRA)
The following dosage and frequency information was taken from the prescribing information for this product: The recommended dosage is 25 mg administered by subcutaneous injection by a professional provider once every 3 months.

REQUIREMENTS
The Company reserves the right to modify the dosing and frequency requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of patisiran (Onpattro) or vutrisiran (Amvuttra). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to, the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of patisiran (Onpattro) or vutrisiran (Amvuttra) outside of the dosing and frequency requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for patisiran (Onpattro) or vutrisiran (Amvuttra).

NOT MEDICALLY NECESSARY

When molecular genetic testing reveals results showing established benign variation(s) or wild-type genotype in the transthyretin (TTR) gene, patisiran (Onpattro) or vutrisiran (Amvuttra)* are considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support their uses as treatments.
* Other than when vutrisiran (Amvuttra) is considered medically necesssary for wild-type ATTR-CM.

EXPERIMENTAL/INVESTIGATIONAL

When molecular genetic testing reveals likely pathogenic or variations of unknown significance (VUS) in the transthyretin (TTR) gene, the use of patisiran (Onpattro) or vutrisiran (Amvuttra) are considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

The use of patisiran (Onpattro) for hATTR amyloidosis with cardiomyopathy in those who are not experiencing polyneuropathy is considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

All other uses for patisiran (Onpattro) and vutrisiran (Amvuttra) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of patisiran (Onpattro) or vutrisiran (Amvuttra) are requested outside of the dosing and frequency requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing patisiran (Onpattro) or vutrisiran (Amvuttra); therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, patisiran (Onpattro) and vutrisiran (Amvuttra) are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

However, services that are identified in this policy as experimental/investigational or not medically necessary are not eligible for coverage or reimbursement by the Company.

PATISIRAN (ONPATTRO)
Patisiran (Onpattro) was approved by the U.S. Food and Drug Administration (FDA) on August 10, 2018, for for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. The safety and effectiveness have not been established in pediatric individuals.

In accordance with FDA prescribing information, patisiran (Onpattro) is administered as an intravenous infusion every 3 weeks. Because of infusion-related reactions, each of the following premedications should be given on the day of infusion, at least 60 minutes prior to the start of infusion (see prescribing information for modifications):

- Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)

VUTRISIRAN (AMVUTTRA)
Vutrisiran (Amvuttra) was approved by the FDA on June 13, 2022, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Supplemental approvals for vutrisiran (Amvuttra) have since been issued by the FDA. The safety and effectiveness have not been established in pediatric individuals.

DIAGNOSTIC TOOLS TO ASSESS AMBULATION

FAMILIAL AMYLOID POLYNEUROPATHY (FAP) STAGES*
The FAP Stages objectively categorize an individual's ability to ambulate into four stages: Stage 0, No symptoms; Stage 1, unimpaired ambulation; Stage 2, assisted ambulation; Stage 3, wheelchair bound or bedridden.

POLYNEUROPATHY DISABILITY (PND) SCORE*
The PND score objectively categorizes an individual's ability to ambulate into six stages.

- Score 0: no impairment

- Score I: preserved walking capacity with sensory disturbances
- Score II: impaired walking, no walking stick or crutch is required
- Score IIIa: one walking stick or crutch is required to walk
- Score IIIb: two walking sticks or crutches are required to walk
- Score IV: confined to wheelchair or bed

*Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.

DIAGNOSTIC TOOLS TO ASSESS HEART FAILURE

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

HEART FAILURE BIOMARKER GUIDELINES
N-terminal pro–brain natriuretic peptide (NT-proBNP) levels are a measure of cardiac stress that is an independent predictor of death in individuals with transthyretin cardiac amyloidosis. Normal NT-proBNP levels vary depending on age, sex, and clinical context. American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of BNP and NT-proBNP to diagnose HF (class I, level of evidence (LOE) A), without indicating specific threshold values. Conversely, European Society of Cardiology (ESC) guidelines recommend the use of BNP and NT-proBNP for the exclusion of HF (class IIa, LOE C), with reference values < 100 ng/L and < 300 ng/L for acute HF, respectively, and < 35 ng/L and < 125 ng/L for chronic HF, respectively. (Castiglione, et al, 2022.)

Description

AMYLOIDOSIS

Amyloidosis is a progressive, degenerative, multisystemic, life-threatening disease in which insoluble fibril proteins (amyloid deposits) accumulate in various organs of the body, including the central nervous system, nerves, gastrointestinal tract, and heart. Transthyretin (TTR) is a protein that is produced in the liver that normally functions to transport thyroid hormone and retinol (vitamin A). There are a few types of amyloidosis, but this section will only discuss transthyretin amyloidosis (ATTR amyloidosis), a condition where TTR misfolds and forms an insoluble fibril protein that deposits itself in various organs of the body. ATTR amyloidosis can be divided into two subtypes:

- Hereditary transthyretin-mediated (hATTR) amyloidosis is caused by a pathogenic variation in the TTR protein. To date, over 120 TTR variants have been identified as a cause of hATTR. The most common being the p.Val30Met mutation found in hATTR with polyneuropathy and Val122Ile mutation found in hATTR with cardiomyopathy.
- Wild-type amyloidosis (wtATTR amyloidosis) is caused by the deposition of misfolded wild-type (normal) TTR. The mechanism of normal TTR causing amyloidosis is unclear.

The majority of TTR mutations cause a “neuropathic” or a “mixed” phenotype; yet, some variants typically manifest with a predominant or isolated cardiomyopathy (Luigetti et al., 2020). Polyneuropathy and cardiomyopathy are progressive and life-threatening, with survival approximately 2 to 15 years after onset of neuropathy and 2 to 5 years after onset of cardiomyopathy.

POLYNEUROPATHY OF HEREDITARY TRANSTHYRETIN-MEDIATED (HATTR) AMYLOIDOSIS
Symptoms commonly develop in the third to fifth decade of life and depend on several factors, including location of the deposits. Examples of symptoms associated with motor, sensory, and autonomic neuropathy include neuropathic pain, carpal tunnel syndrome, muscle weakness that affects daily living, orthostatic hypotension, recurrent urinary tract infections, diarrhea, nausea, vomiting, vision disorders (e.g., vitreous opacity, dry eyes, glaucoma, or pupils with an irregular or scalloped appearance), cardiac conduction blocks, and arrhythmias. Symptoms of hATTR can cause severe decreased ambulation, decline in daily function due to pain or discomfort, and anxiety or depression.

WILD-TYPE OR HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH CARDIOMYOPATHY (ATTR-CM)
Symptoms commonly develop in individuals at least 60 years of age and older (more commonly in those over 70 years of age). Examples of symptoms associated with cardiac amyloidosis include dyspnea, lower extremity edema, elevated jugular venous pressure, hepatic congestion, ascites, and syncope or presyncope. Additionally, autonomic or peripheral nerve disease can develop.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Patisiran (Onpattro) was the first pharmacologic treatment approved by the US Food and Drug Administration (FDA) for the treatment of adults with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis. Prior to its approval, treatment options consisted of orthotopic liver transplant or a TTR tetramer stabilizer, such as diflunisal (as an off-label indication). Since its approval, other treatments have been approved by the FDA (e.g., inotersen [Tegsedi], vutrisiran [Amvuttra]).

Additionally, vutrisiran (Amvuttra) was approved by the FDA for cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR) in 2025.

Patisiran (Onpattro) and vutrisiran (Amvuttra) represent a class of drugs called double-stranded small interfering ribonucleic acid (siRNA) treatment that controls gene expression by silencing or interfering with a targeted portion of RNA to reduce the amount of disease-causing TTR, causing a reduction in the amount of amyloid deposits in the body. Patisiran (Onpattro) is administered by intravenous infusion every 3 weeks. Vutrisiran (Amvuttra) is administered by a professional provider by subcutaneous injection once every 3 months.

PATISIRAN (ONPATTRO)
Peer-Reviewed Literature

Summary

Polyneuropathy of Hereditary Transthyretin-mediated (hATTR) amyloidosis
APOLLO was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and effectiveness of patisiran (Onpattro) in 225 adults with hATTR amyloidosis. Participants were required to have a documented pathogenic variant in *TTR*, a Neuropathy Impairment Score (NIS) of 5 to 130 (range, 0–244, with higher scores indicating more impairment) and a polyneuropathy disability score of IIIb or lower (with higher scores indicating more impaired walking ability). Participants were randomly assigned (2:1) to either patisiran (Onpattro), 0.3 mg/kg, or placebo via intravenous infusion once every 3 weeks for 18 months. The primary efficacy endpoint was the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7). The study resulted in a reduction in TTR level by 81% in those treated with patisiran (Onpattro). There was a statistically significant improvement in polyneuropathy (mNIS+7 score) in those treated with patisiran (Onpattro) compared to placebo. At 18 months, 56% of participants treated with patisiran (Onpattro) had improvement in mNIS+7, compared with 4% treated with placebo.

The following secondary endpoints showed statistically significant improvement in those treated with patisiran (Onpattro): quality of life (Norfolk Quality of Life–Diabetic Neuropathy [Norfolk QOL-DN] questionnaire), motor strength (NIS-weakness); disability (Rasch-built Overall Disability Scale [R-ODS]), gait speed (10-meter walk test), nutritional status (modified body mass index [BMI]), patient-reported autonomic symptoms (Composite Autonomic Symptom Score). Exploratory endpoints were evaluated in a predefined cardiac subpopulation that showed improvement in echocardiographic measures of cardiac structure and function and a reduction in N-terminal pro–brain natriuretic peptide (NT-proBNP) levels (a measure of cardiac stress that is an independent predictor of death in individuals with transthyretin cardiac amyloidosis) in those treated with patisiran (Onpattro). The frequency of severe adverse events and serious adverse events were similar between the two groups.

VUTRISIRAN (AMVUTTRA)

Peer-Reviewed Literature
Summary

<u>Wild-Type or Hereditary Transthyretin amyloidosis with cardiomyopathy (ATTR-CM)</u>

HELIOS-B was a Phase 3, global, multicenter, double-blind, randomized, placebo-controlled study that evaluated the safety and effectiveness of vutrisiran (Amvuttra) in 655 adults with ATTR-CM (either hereditary ATTRv [v for variant] or wild-type ATTR [ATTRwt]), defined as the presence of TTR amyloid deposits in a tissue-biopsy specimen or fulfillment of validated scintigraphy-based diagnostic criteria for ATTR-CM in the absence of monoclonal gammopathy; and evidence of cardiac involvement as assessed with transthoracic echocardiography, with an end-diastolic interventricular septal wall thickness exceeding 12 mm. Participants had a clinical history of heart failure, with at least one previous hospitalization for heart failure or clinical evidence of heart failure, with signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment. At baseline, participants were either receiving tafamidis or were not receiving tafamidis, with no active plan to start tafamidis during the first 12 months after randomization. Those who were not receiving tafamidis at baseline could receive it

after enrollment, if necessary. Additional inclusion criteria were an NT-proBNP level of more than 300 pg per milliliter and less than 8500 pg per milliliter (or >600 pg per milliliter and <8500 pg per milliliter for patients with atrial fibrillation) and the ability to cover a distance of at least 150 m on the 6-minute walk test. Key exclusion criteria were a New York Heart Association (NYHA) class of IV, or a NYHA class of III with a National Amyloidosis Centre ATTR stage of 3 (defined as an NT-proBNP level of >3000 pg per milliliter and an estimated glomerular filtration rate [eGFR] of <45 ml per minute per 1.73 m^2 of body-surface area); a polyneuropathy disability score of IIIa, IIIb, or IV (indicating that a cane or stick is needed to walk or that the patient is wheelchair-bound); cardiomyopathy that was not associated with ATTR amyloidosis; and an eGFR of less than 30 ml per minute per 1.73 m^2. Participants were randomly assigned (1:1) to treatment with vutrisiran (Amvuttra) 25 mg SC or placebo SC every 12 weeks for up to 36 months. All the end points were assessed separately in the overall population and in the monotherapy population (those who were not receiving tafamidis at baseline), resulting in 10 prespecified end points for analysis (2 primary and 8 secondary). The primary end point was a composite of death from any cause and recurrent cardiovascular (CV) events (defined as hospitalizations for CV causes or urgent visits for heart failure) during the double-blind period (up to 36 months). Treatment with vutrisiran (Amvuttra) led to a statistically significant reduction in the risk of death from any cause and recurrent CV events compared to placebo in the overall and monotherapy population of 28% and 33%, respectively(hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; P = 0.01; hazard ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; P = 0.02). Vutrisiran (Amvuttra) also preserved functional capacity and quality of life and prevented worsening of heart failure symptoms. These effects were consistent across all prespecified subgroups, including individuals who were receiving background tafamidis. The incidence of adverse events was similar between the groups.

Among the participants in the monotherapy population, 44 out of 196 (22%) in the vutrisiran (Amvuttra) group and 41 out of 199 (21%) in the placebo group began tafamidis treatment after randomization. The study lacks stratified data to assess outcomes specifically for individuals who did not receive tafamidis at baseline and did not start tafamidis after randomization (i.e., there is no explicit and individualized outcome data for individuals who only received vutrisiran (Amvuttra) throughout the study), nor is there stratified data available for individuals who received Amvuttra and started tafamidis after randomization. The peer-reviewed published data have been reported in an overall manner at this point. The authors reported data stratified by baseline tafamidis use in the overall population even though a portion of individuals not receiving tafamidis at baseline did in fact go on to receive tafamidis at some point during the study. Among participants in the overall population, those given vutrisiran (Amvuttra) who were not receiving tafamidis at baseline had a 33% lower risk of death from any cause and recurrent cardiovascular events compared to placebo (hazard ratio = 0.67; 95% CI, 0.49 to 0.93), whereas, those given vutrisiran (Amvuttra) who were receiving tafamidis at baseline had a 21% lower risk of the composite endpoint compared to placebo (hazard ratio = 0.79; 95% CI, 0.51 to 1.21). Since the current seminal work does not have results reported in a stratified manner (including participants that may have had vutrisiran (Amvuttra) only throughout the trial), additional data would be needed to assess the effectiveness and/or additional clinical value that may result from tafamidis + vutrisiran (Amvuttra) combination therapy. Concurrent use of Amvuttra with other medications indicated for the treatment of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy have yet to be studied.

Polyneuropathy of Hereditary Transthyretin-mediated (hATTR) amyloidosis

HELIOS-A was a Phase 3, global, multicenter, randomized, open-label study that evaluated the safety and effectiveness of vutrisiran (Amvuttra) in 160 adults with hereditary transthyretin (ATTRv; v for variant) amyloidosis (also known as hATTR amyloidosis). Participants were required to have a documented pathogenic variant in *TTR*, a NIS of 5 to 130, a polyneuropathy disability (PND) score of IIIb or less, a Karnofsky Performance Status score of 60% or greater, and adequate liver and renal function. Participants were randomly assigned (3:1) to treatment with vutrisiran (Amvuttra) 25 mg SC every 3 months or patisiran (Onpattro) 0.3 mg/kg IV every 3 weeks for 18 months or external placebo group from the APOLLO study. The primary efficacy endpoint was the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7) compared with the placebo group of the APOLLO study (external placebo group) at Month 9. The study resulted in with vutrisiran (Amvuttra) meeting the primary endpoint, resulting in statistically significant improvement in mNIS+7 at Month 9 versus the external placebo group. At Month 9, 50.4% of participants treated with vutrisiran (Amvuttra) had an improvement in mNIS+7 versus 18.2% in the external placebo group. Vutrisiran (Amvuttra) met all of its secondary efficacy endpoints: significant improvements versus external placebo were observed in Norfolk Quality of Life-Diabetic Neuropathy, 10-meter walk test (both at 9 and 18 months), mNIS+7, modified body-mass index, and Rasch-built Overall Disability Scale (all at 18 months). TTR reduction with vutrisiran (Amvuttra) every 3 months was noninferior to within-study patisiran (Onpattro) every 3 weeks. Most adverse events were mild or moderate in severity, and consistent with ATTRv amyloidosis natural history. There were no drug-related discontinuations or deaths. All secondary endpoints resulted in significant improvements with vutrisiran (Amvuttra) treatment compared with the external placebo group.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord*. 2013;6(2):129-139.

Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med*. 2018;379(1):11-21.

Adams D, Tournev IL, Taylor MS, et al.; HELIOS-A Collaborators. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2022;23:1-9.

American Heart Association. Classes and Stages of Heart Failure. 05/21/2025. Available at: Classes and Stages of Heart Failure | American Heart Association. Accessed June 24, 2025.

American Hospital Formulary Service (AHFS). Drug Information 2025. Patisiran (Onpattro). [Lexicomp Online Web site]. 07/25/2022. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed April 11, 2025.

American Hospital Formulary Service (AHFS). Drug Information 2025. Vutrisiran (Amvuttra). [Lexicomp Online Web site]. 01/16/2023. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed April 11, 2025.

Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.

Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Fail Rev*. 2022 Mar;27(2):625-643.

Elsevier's Clinical Pharmacology Compendium. Patisiran (Onpattro). 03/21/2025. [Clinical Key Web site]. Available at: https://www.clinicalkey.com/pharmacology/ [via subscription only]. Accessed April 11, 2025.

Elsevier's Clinical Pharmacology Compendium. Vutrisiran (Amvuttra). 03/24/2025. [Clinical Key Web site]. Available at: https://www.clinicalkey.com/pharmacology/ [via subscription only]. Accessed April 11, 2025.

Fontana M. Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis. [UpToDate Web Site]. Updated 05/02/2024. Available at: Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis - UpToDate [via subscription only]. Accessed April 30, 2025.

Fontana M. Cardiac amyloidosis: Treatment and prognosis. [UpToDate Web Site]. Updated 02/06/2025. Available at: Cardiac amyloidosis: Treatment and prognosis - UpToDate [via subscription only]. Accessed April 30, 2025.

Fontana M, Berk JL, Gillmore JD, et al; HELIOS-B Trial Investigators and Collaborators. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. *N Engl J Med*. 2025 Jan 2;392(1):33-44.

Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care*. 2017;23(7 Suppl):S107-S112.

Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J.* 2018 Aug 7;39(30):2799-2806.

Lexi-Drugs Compendium. Patisiran (Onpattro). 11/05/2024. [Lexicomp Online Web site]. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed April 11, 2025.

Lexi-Drugs Compendium. vutrisiran (Amvuttra). 04/03/2025. [Lexicomp Online Web site]. Available

at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed April 11, 2025.

Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. *Ther Clin Risk Manag*. 2020;16:109-123.

National Institutes of Health (NIH). Genetics Home Reference. Transthyretin amyloidosis. Reviewed 11/08/2023. Available at: https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis. Accessed August 23, 2024.

Patisiran (Onpattro). [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; 01/2023. Available at: https://www.onpattro.com/. Accessed April 11, 2025.

Truven Health Analytics. Micromedex® DrugDex® Compendium. Patisiran (Onpattro). 02/27/2025. Greenwood Village, CO. [Micromedex® Solutions Web site]. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [via subscription only]. Accessed April 11, 2025.

Truven Health Analytics. Micromedex® DrugDex® Compendium. vutrisiran (Amvuttra). 03/25/2025. Greenwood Village, CO. [Micromedex® Solutions Web site]. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [via subscription only]. Accessed April 11, 2025.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Patisiran (Onpattro) prescribing information and approval letter [FDA Web site]. 01/13/2023. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 11, 2025.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Vutrisiran (Amvuttra) prescribing information and approval letter [FDA Web site]. 03/20/2025. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 11, 2025.

Vutrisiran (Amvuttra). [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; 03/2025. Available at: https://www.amvuttra.com/. Accessed April 11, 2025.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.
Pre

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)

J0222 Injection, Patisiran, 0.1 mg
J0225 Injection, Vutrisiran, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.100e:

09/16/2025	This version of the policy will become effective 09/16/2025. This policy was updated to include the coverage criteria for vutrisiran (Amvuttra) for the treatment of Wild-Type or Hereditary Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults. All of the ICD-10 CM codes have been removed from this policy, since they are informational. Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

Revisions From MA08.100d:

12/16/2024	This version of the policy will become effective 12/16/2024. The policy was updated to include an example of a drug similar to Onpattro and Amvuttra, called eplontersen (Wainua). Additionally, the following Note has been added to the Policy Section: NOTE: Evio has been selected by the Company to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies. Patisiran (Onpattro) and vutrisiran (Amvuttra) are included in the portfolio of high-cost drug therapies for which Evio will be tracking clinical outcomes. If a patient meets all medical policy provisions and is approved to receive treatment, the requesting professional provider or member must attest and agree to providing clinical outcomes data and information via Evio's secure web portal as requested.

Revisions From MA08.100c:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
06/12/2023	This version of the policy will become effective 06/12/2023. The policy was updated to include the coverage criteria for vutrisiran (Amvuttra), approved by the US Food and Drug Administration (FDA) on June 13, 2022 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Criteria revisions include: • Expanding the provider type to include geneticist, or professional providers specializing in the treatment of amyloidosis • Clarifying that the individual is unlikely to be a candidate for liver transplant • Restriction of combination therapy with patisiran (Onpattro), vutrisiran (Amvuttra), or any other RNA interference agents (e.g., inotersen [Tegsedi]), or Transthyretin stabilizers (e.g., tafamidis [Vyndaqel, Vyndamax]) The following HCPCS code has been **added** to this policy: J0225 Injection, Vutrisiran, 1 mg

Revisions From MA08.100b:

11/16/2022	This policy has been reissued in accordance with the Company's annual review process.
11/17/2021	This policy has been reissued in accordance with the Company's annual review process.

12/16/2020	This policy has been reissued in accordance with the Company's annual review process.
10/01/2019	This policy has been identified for the HCPCS code update, effective 10/01/2019. The following HCPCS codes have been **removed** from this policy: C9036 Injection, patisiran, 0.1 mg J3490 Unclassified drugs The following HCPCS code has been **added** to this policy: J0222 Injection, Patisiran, 0.1 mg

Revisions from MA08.100a:

09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
01/01/2019	This policy has been identified for the HCPCS code update, effective 01/01/2019. The following HCPCS code has been **added** to this policy: C9036 Injection, patisiran, 0.1 mg The following HCPCS code has been **removed** from this policy: C9399 Unclassified drugs or biologicals

Revisions from MA08.100:

11/19/2018	This new policy has been issued to communicate the Company’s coverage position.

Version Effective Date:
09/16/2025
Version Issued Date:
09/16/2025
Version Reissued Date:
N/A