P&T Date: 06/05/2025

# **Amvuttra™®** (vutrisiran)

**HCPCS:** J0225

**Policy:**

*Requests must be supported by submission of chart notes and patient specific documentation.*

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy(formerly known as familial amyloid polyneuropathy or FAP) and ALL of the following:
      i. Documentation of TTR gene mutation
      ii. Signs and symptoms of ocular or cerebral area involvement (such as in ocular amyloidosis or primary/leptomeningeal amyloidosis), if present, must not predominate over polyneuropathy symptomology associated with hATTR
      iii. Documentation of clinical signs and symptoms of peripheral neuropathy (such as: tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking)
      AND/OR
      Documentation of clinical signs and symptoms of autonomic neuropathy symptoms (such as: orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety])
      iv. Must have a baseline polyneuropathy disability (PND) score ≤ IIIb and/or baseline FAP Stage 1 or 2
   c. Diagnosis of wild-type or variant (hereditary) transthyretin-mediated amyloidosis with cardiomyopathy (ATTR-CM) and ALL of the following:
      i. ATTR-CM diagnosis must be confirmed by ONE of the following:
         1. A negative monoclonal light chain screen ruling out amyloid light chain cardiomyopathy AND technetium-labeled bone scintigraphy, OR
         2. Endomyocardial biopsy with confirmatory transthyretin amyloid typing by mass spectrometry, immunoelectron microscopy, or immunohistochemistry
      ii. For variant ATTR-CM, diagnosis must also be confirmed by documentation of TTR gene mutation
      iii. Documentation of clinical signs and symptoms of ATTR-CM, including NYHA Class I, II, or III heart failure characterized by limited functional capacity and decline in quality of life
      iv. Trial and failure, contraindication, or intolerance to a transthyretin stabilizer indicated for ATTR-CM, such as Vyndaqel®, Vyndamax®, or Attruby®

d. Amvuttra will not be used in combination with other therapies approved for transthyretin-mediated amyloidosis
e. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in WyoBlue Advantage's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
a. Quantity Limits: Align with FDA recommended dosing
b. Authorization Period: One year at a time
c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit.

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

**Background Information:**

- Amvuttra is a transthyretin (TTR) silencer indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, and for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations, and urgent heart failure visits.

- Transthyretin amyloidosis (ATTR) is a progressive, life-threatening disorder characterized by the deposition of amyloid fibrils composed of TTR, a plasma transport protein for thyroxine and vitamin A that is predominantly produced by the liver and to a lesser extent by the choroid plexus and in retinal cells.

- In ATTR, TTR misfolds, causing it to aggregate into amyloid fibrils that accumulate in organs, nerves, and tissues. The buildup of these amyloid deposits results in progressive dysfunction at the site of deposition. Amyloid deposition can occur in the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral nervous system, and central nervous system. The phenotype is driven by deposition site and may be predominantly cardiac, neurologic, or mixed.

- There are two types of ATTR: hereditary (hATTR), or variant, which is due to inherited mutations of the TTR gene that cause misfolding of the tetramer subunits, and wild-type, which occurs in the presence of a normal TTR gene, is typically associated with aging, and is most often diagnosed in men 65 years and older. In wild-type ATTR, TTR typically only deposits in the heart and manifests as cardiac symptoms. hATTR, in contrast, may be predominantly neuropathic, cardiomyopathy, or a mixed phenotype characterized by both.

- hATTR with polyneuropathy (hATTR-PN)

    - hATTR-PN is the most common neurologic manifestation. Without treatment, patients will have progressive neuropathy and disability ultimately resulting in death within 10-15 years of disease onset.

    - Patients with hATTR-PN may present with peripheral neuropathy (sensory and motor; tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy (e.g., orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety]), GI impairment,

cardiomyopathy, nephropathy, or ocular deposition. Most hATTR-PN cases, however, are classified as neuropathic.

- Amyloid deposition induces a length-dependent peripheral neuropathy beginning in the lower limbs with symptoms like toe discomfort due to numbness and spontaneous pain. Continued aggregation of amyloid on the nerve fibers contributes to sensory loss extending upwards toward the proximal lower limbs as motor deficits and impaired sensations occur. Walking becomes increasingly difficult as balance and gait are affected. Neuropathic pain transitions to a burning sensation worsening at night. Over time, sensory deficit extends to the upper limbs, forearms, fingers and trunk and motor deficit follows with the same length dependent progression. At this stage, potentially life-threatening autonomic dysfunction is present manifesting as orthostatic hypotension, anhidrosis, neurogenic bladder, disturbances of gastrointestinal motility, and sexual impotence.

- Cardiac disease may occur in approximately 50% of patients with hATTR-PN. Ocular involvement is also common, including vitreous opacity, dry eye, glaucoma, and pupillary disorder.

- A rarer presentation of hATTR is leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity (oculoleptomeningeal amyloidosis). Several mutations have reportedly been linked to this type of hATTR, though it may also manifest in more advanced cases of *Val30MET*-mutated hATTR-PN.

    - Central nervous system symptoms include stroke, subarachnoid hemorrhage, dementia, ataxia, seizures, and sensorineural hearing loss.

    - The source of mutant TTR in (oculo)leptomeningeal and meningovascular amyloidosis is thought to be the choroid plexus and retinal cells versus the liver. As such, ocular and meningovascular manifestations are commonly seen after liver transplantation because the source of mutant TTR is left unaffected.

    - To date, no treatments have been proven to be beneficial for the treatment of (oculo)leptomeningeal and meningovascular amyloidosis.

- The 2013 guideline of transthyretin-related hereditary amyloidosis for clinicians recommends that the most reliable diagnostic approach involves genetic testing and tissue biopsy to confirm the presence of active amyloid formation. Genetic testing is needed to document the TTR gene mutations; if testing is normal, a diagnosis of hATTR is excluded.

- Options for hATTR-PN treatment are limited. Treatment strategies include removing the source of mutant TTR, inhibiting TTR formation, stabilizing the TTR molecule, and therapy directed at removing the amyloid deposits. Regardless of the choice of treatment, the 2013 guidelines and published expert opinion from 2024 recommend treatment initiation as soon as possible after diagnosis to slow or halt disease progression. The best outcomes have been shown in patients diagnosed at younger ages and/or without advanced disease.

- For hATTR-PN, our best treatment option historically had been orthoptic liver transplant, which removes the source of mutant TTR and was considered the gold standard for hATTR-PN treatment early in the course of disease. In hATTR-PN, the liver is the primary source of mutant TTR; transplantation eliminates approximately 95% of the production of mutant TTR and may slow or halt disease progression outside of the brain and/or eyes, though nerve function rarely improves post-transplant. Transplant does not effectively prevent cardiomyopathy, however, and is not recommended for patients with late stage hATTR-PN or leptomeningeal disease. With later stages of hATTR-PN and cardiomyopathy, there are concerns of disease

progression due to deposition of wild-type TTR from the transplanted liver on the preexisting amyloid from the variant TTR

- Numerous disease-modifying therapeutics are now available for hATTR-PN, including Amvuttra (vutrisiran), Onpattro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpattro, Tegsedi, and Wainua specifically; however, they do note that early detection is critical and patients with early-stage disease should be treated with any approved drugs as they become available and as the patient's disease state meets drug indications, independent of liver transplant plans.

- Amvuttra, Onpattro, Tegsedi, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Wainua is FDA approved to be administered by the patient or caregiver, while a healthcare provider is required for Amvuttra and Onpattro administration per approved labeling. To date, there is no literature supporting the use of one product over another, nor is there support for the use of any of these products together or in combination with other therapies approved for ATTR. The 2024 expert opinion does not offer recommendations on choice of specific treatment due to the lack of direct comparison trials and advises that clinicians consider the efficacy and safety considerations, in addition to any comorbidities and personal preferences around ease of use for an individual patient.

- Amvuttra is a small interfering ribonucleic acid agent (siRNA) targeting TTR that silences a portion of RNA involved in causing the disease. Amvuttra is designed to deliver the drug directly into the liver to interfere with RNA production of an abnormal form of TTR, ultimately reducing accumulation of amyloid deposits in peripheral nerves.

    - In the pivotal phase 3 HELIOS-A trial, Amvuttra demonstrated better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to an external placebo group from patisiran's pivotal APOLLO trial. Amvuttra-treated patients also scored better on assessments of walking, nutritional status, and the ability to perform activities of daily living. Amvuttra also demonstrated non-inferiority in serum TTR reduction relative to the within-study patisiran reference group, which showed results consistent to the Amvrutta-treated group throughout the study.

    - In clinical trials, Amvuttra was only evaluated in patients with a baseline polyneuropathy disability (PND) score $\leq$IIIb, which equates to a familial amyloidotic polyneuropathy (FAP) stage of 1 or 2. The PND score (range 0-IV) stages disease based on walking ability, while the FAP stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy. Amvuttra was not evaluated in patients with baseline PND score of IV which, like FAP stage 3, designates patients with late-stage, significantly advanced disease who are wheelchair-bound or bedridden, therefore clinical trials do not support use in this patient population with advanced disease.

    - Patients who received prior TTR-lowering treatment and those with a history of liver transplant were also excluded from clinical trials of Amvuttra. There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Amvuttra as they would not be expected to produce mutated TTR post-transplant.

- ATTR with cardiomyopathy (ATTR-CM)

    - Patients with ATTR-CM are typically males aged 65 years or older. The condition may be inherited or occur sporadically sans inheritance pattern due to wild-type (or normal) TTR.

- In ATTR-CM, the left ventricle ejection fraction is normal or only mildly reduced and coupled with ventricular hypertrophy. Amyloid deposition commonly affects the conduction system as well, leading to bundle branch block and on occasion atrioventricular and sinoatrial block. Pacemaker implantation is often required. Typical signs and symptoms include dyspnea, lower extremity edema, elevated jugular venous pressure, hepatic congestion, and ascites. In more advanced disease, signs and symptoms of low cardiac output may also occur (e.g., diminished pulse pressure and capillary refill). ATTR-CM progresses rapidly, with a life expectancy of 3 to 5 years from diagnosis, depending on the subtype.

- Clinical suspicion for cardiac amyloidosis includes left ventricular wall thickening (thickness > 14 mm) in conjunction with fatigue, dyspnea, or edema, especially in the context of discordance between wall thickness on echocardiogram and ECG voltage, and in the context of aortic stenosis, heart failure with preserved ejection fraction (HFpEF), carpal tunnel syndrome, spinal stenosis, and autonomic or sensory polyneuropathy.

- The 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guideline for the management of heart failure and the 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient with Cardiac Amyloidosis provide the most up to date recommendations for the diagnosis and treatment of patients with cardiac amyloidosis.

- In patients with the above features, it is important to differentiate between amyloid light chain cardiomyopathy (AL-CM) and ATTR-CM. Per both guidelines, this is done by screening for the presence of serum and urine monoclonal light chains. AL-CM can be ruled out by obtaining a monoclonal light chain screen assessing serum free light chain (sFLC) concentration and serum and urine immunofixation electrophoresis (IFE). If no monoclonal light chains are detected then AL-CM is excluded and technetium-labeled bone scintigraphy is performed to confirm the presence of ATTR-CM. Scans may be positive even in AL-CM; therefore, a bone scintigraphy scan alone cannot distinguish ATTR-CM from AL-CM without concomitant light-chain testing.

- Endomyocardial biopsy is an additional, though more invasive, option for diagnosis and is recommended in situations where there is high clinical suspicion of ATTR-CM in patients with abnormal monoclonal light chain screening, high clinical suspicion of ATTR-CM in patients with negative or questionable scintigraphy results, or in the event cardiac scintigraphy is not available. Amyloid deposits detected on biopsy are then identified, or typed, by mass spectrometry, immunoelectron microscopy or immunohistochemistry to determine whether the precursor protein is TTR.

- If ATTR-CM is identified, genetic sequencing of the TTR gene is performed to determine if the patient has hereditary or wild-type disease. This differentiation is important in triggering genetic counseling, screening family members, and potentially identifying appropriate pharmacologic therapies.

- For patients with ATTR-CM, hereditary or wild-type, and exhibiting NYHA class I-III symptoms, the 2022 guidelines recommend treatment with tafamidis. Tafamidis is approved under the brand names Vyndaqel® and Vyndamax® for the treatment of adults with ATTR-CM to reduce cardiovascular mortality and cardiovascular-related hospitalization. It works by stabilizing TTR to prevent it from misfolding and subsequently creating amyloid deposits. It should be noted that tafamidis prevents but does not reverse amyloid deposition; therefore, its greatest benefit is anticipated when administered early in the disease course. The 2023 ACC consensus statement aligns with the 2022 guidelines, recommending that tafamidis remain the first-line agent to treat ATTR-CM as at the time of publication it was the only available FDA approved drug for this indication.

- In December 2024, the FDA approved Attruby (acoramidis) for the treatment of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization. Attruby is a

transthyretin stabilizer like tafamidis. Though it boasts a near-complete (> 90%) stabilization of TTR, the clinical significance of this finding is uncertain as there is insufficient evidence associating TTR levels and degree of stabilization with improved clinical outcomes. Amvuttra is the third agent approved for ATTR-CM and has a novel mechanism of action in this category, inhibiting hepatic synthesis of both wild-type and variant TTR mRNA at the source to prevent the protein from forming in the first place. Guidelines have not yet been updated to include either Attruby or Amvuttra.

- In the pivotal Phase III HELIOS-B clinical trial, 645 patients with either wild-type or hereditary ATTR-CM and a history of heart failure (NYHA Class I-III) received either Amvuttra or placebo once every 3 months for up to 36 months. Patients with NYHA Class IV or high-risk Class III (i.e., NT-proBNP level>3,000 pg/mL and eGFR <45 mL/min/1.73m$^2$ of body-surface area), or a PND of IIIa, IIIb, or IV (indicating a cane or stick is needed to walk, or that a patient is wheelchair-bound) were excluded. At baseline, 40% of patients were established on tafamidis, and participants were permitted to initiate open-label tafamidis during the study. Treatment with Amvuttra led to significant reduction in the risk of all-cause mortality and recurrent cardiovascular events compared to placebo in the overall and monotherapy populations of 28% and 33%, respectively.

- Though HELIOS-B represents the most robust data currently available on concurrent TTR silencer and TTR stabilizer use, the trial was not designed to determine the differences between monotherapy and combination therapy. Therefore, there is insufficient evidence to distinguish the net health benefit among the drugs when used as monotherapy or to support the use of combination therapy in ATTR-CM. Additionally, there is no literature to date supporting the use of Amvuttra in combination with other therapies approved for ATTR, such as Onpattro, Wainua, or Attruby.

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| Policy History | | |
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| # | Date | Change Description |
| 1.0 | Initial Effective Date: 01/01/2026 | New policy |

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*