Blue Cross Blue Shield Blue Care Network of Michigan

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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 06/11/2026

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

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 BCBSM/BCN'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, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Wainua autoinjector is FDA approved to be administered by the patient or caregiver, while a healthcare provider is required for Amvuttra, Onpattro, and Wainua prefilled syringe 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 $\geq$ 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), or extracardiac manifestations such as bilateral carpal tunnel syndrome, lumbar/cervical spinal stenosis, spontaneous biceps tendon rupture, hip or knee replacement, and autonomic or sensory polyneuropathy. Extracardiac manifestations often precede cardiac involvement by many years, with nearly 80% of individuals with ATTR-CM having preceding orthopedic interventions of the shoulder, hip, or knee, carpal tunnel syndrome, spinal stenosis, trigger finger, or biceps tendon rupture due to extracardiac TTR amyloid deposition.

- The 2025 American College of Cardiology Concise Clinical Guidance on transthyretin cardiac amyloidosis evaluation and management provides the most up to date recommendations for the diagnosis and treatment of patients with cardiac amyloidosis.

- In patients with the above features, it is critical to differentiate between amyloid light chain cardiomyopathy (AL-CM) and ATTR-CM. Per the 2025 guidance, 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); a combination of these three tests has a 99% sensitivity for detecting amyloid light chain amyloidosis. 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 confirmed ATTR-CM, either hereditary or wild-type, with a clinical history of heart failure and exhibiting NYHA class I-III symptoms, the 2025 guidance recommends initiation of disease-modifying therapies for ATTR-CM. To date, two transthyretin stabilizers (tafamidis and acoramidis) and one transthyretin silencer (vutrisiran) have been approved by the FDA for ATTR-CM. Transthyretin stabilizers stabilize TTR to prevent it from misfolding and subsequently creating amyloid deposits, while transthyretin silencers degrade TTR mRNA in hepatocytes to reduce the production of TTR. These therapies prevent but

do not reverse amyloid deposition and any related end-organ damage; therefore, their greatest benefit is anticipated when administered early in the disease course.

- The 2025 guidance does not recommend one ATTR-CM therapy over another and instead advises that the choice of ATTR-CM treatment should be based on individualized factors such as cost, access, and patient or provider preference. Available clinical data does not justify the use of combination therapy with either two TTR stabilizers or a combination of a TTR silencer and stabilizer

- 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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<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.6</td><td>Effective Date: 07/27/2026

P&T Date: 06/11/2026</td><td>Removed criteria requiring trial and failure, contraindication, or intolerance to a transthyretin stabilizer indicated for ATTR-CM to instead leverage the trial and failure of preferred criterion for enforcing step therapy requirement</td></tr>
<tr><td>1.5</td><td>Effective Date: 06/05/2025</td><td>Added criteria for new ATTR-CM indication

Reworded diagnosis criteria for clarity to align with approved labeling

Removed hATTR-PN criteria preventing use with NYHA class >2 since Amvuttra can now be used for cardiomyopathy in patients beyond class 2

Removed criteria preventing use with previous liver transplant to align with management for other ATTR therapies</td></tr>
<tr><td>1.4</td><td>Effective Date: 08/08/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 08/10/2023</td><td>Annual review of criteria performed, no changes were made</td></tr>
<tr><td>1.2</td><td>Effective Date: 08/08/2022</td><td>UM medical management system update for MAPPO and BCNA

<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.1</td><td>Effective Date: 08/04/2022</td><td>New Policy</td></tr>
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** 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.*

Blue Cross Blue Shield/Blue Care Network of Michigan Medication Authorization Request Form
Amvuttra™ (vutrisiran) HCPCS CODE: J0225

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for Amvutra™. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION		PHYSICIAN INFORMATION
Name		**Name**
ID Number		**Specialty**
D.O.B.	☐Male ☐Female	**Address**
Diagnosis		**City /State/Zip**
Drug Name	☐Amvuttra™	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**Weight (kg)**	**NPI**
Directions		**Contact Person**
Date of Service(s)		**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation *Date patient started therapy:* _____

2. Please provide the NPI number for the place of administration: _____

3. **Initiation AND Continuation of therapy:**
   a. Does the patient have peripheral neuropathy caused by hereditary transthyretin amyloidosis (hATTR) with a documented TTR mutation? ☐ Yes ☐ No Comment _____
   b. Please check off the symptoms of neuropathy the patient is experiencing: ☐ Tingling/pain in the hands/feet/arms ☐ Numbness/tingling in the wrists ☐ Carpal tunnel syndrome ☐ Loss of ability to sense temperature ☐ Weakness in legs/difficulty walking ☐ Difficulty with fine motor skills ☐ Orthostasis ☐ Abnormal sweating ☐ Constipation/diarrhea ☐ Nausea/vomiting ☐ Anorexia/early satiety ☐ Loss of feeling in the hand and/or feet ☐ Other: _____
   c. Does the patient have any signs or symptoms of ocular amyloidosis or primary/leptomeningeal amyloidosis? ☐ Yes ☐ No
      i. If Yes, do these predominate over polyneuropathy symptomology? ☐Yes ☐No Comment _____
   d. What is the patient's PND score before starting Amvuttra? ☐ 0 ☐ I ☐ II ☐ IIIA ☐ IIIB ☐ IV
   e. What is the patient's FAP stage before starting Amvuttra? ☐ 0 ☐ 1 ☐ 2 ☐ 3
   f. Will the patient be using Amvuttra in combination with other therapies approved for transthyretin-mediated amyloidosis? ☐ Yes ☐ No Comment _____
   g. Has the patient had a prior liver transplant? ☐ Yes ☐ No
   h. Does the patient have heart failure? ☐ Yes ☐No If Yes: New York Heart Association Class ☐ I ☐ II ☐ III ☐IV

4. **Continuation of therapy:**
   a. Has the patient's condition improved while on therapy with Amvuttra? ☐ Yes ☐ No Comment _____

Please add any other supporting medical information necessary for our review

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	**Physician Signature**	**Date**
Step 2: Checklist	☐ Form Completely Filled Out ☐ Attached Chart Notes	
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

8/4/2022; 10/5/2022