Clinical Policy: Vutrisiran (Amvuttra)

Reference Number: PA.CP.PHAR.550
Effective Date: 05/2023
Last Review Date: 04/2026

Description
Vutrisiran (Amvuttra™) is a transthyretin-directed small interfering ribonucleic acid (RNA).

FDA Approved Indication(s)
Amvuttra is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Amvuttra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hereditary Transthyretin-Mediated Amyloidosis (must meet all)**:**

1. Diagnosis of hATTR with polyneuropathy;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Documentation confirms presence of a transthyretin (TTR) mutation;
5. One of the following (a or b):
   a. Biopsy is positive for amyloid deposits;
   b. Medical justification is provided as to why treatment should be initiated despite a negative biopsy or no biopsy;
6. Member has not had a prior liver transplant;
7. Amvuttra is not prescribed concurrently with Onpattro or Wainua;
8. Dose does not exceed 25 mg every 3 months.

Approval duration: 12 months

B. Transthyretin Amyloid Cardiomyopathy (must meet all)**:**

1. Diagnosis of ATTR-CM;
2. Prescribed by or in consultation with a cardiologist;
3. Age ≥ 18 years;
4. Diagnosis is supported by one of the following (a or b):
   a. Tissue biopsy amyloid protein is identified as transthyretin via mass spectrometry or immunohistochemistry, and (i or ii):
      i. Tissue biopsy is of endomyocardial origin;
      ii. Tissue biopsy is of extra-cardiac origin and echocardiography (Echo), cardiac magnetic resonance imaging (CMR), or positron emission tomography (PET) findings are consistent with cardiac amyloidosis;
   b. Member meets all of the following (i, ii, and iii):

i. Echo, CMR, or PET findings are consistent with cardiac amyloidosis;
ii. Cardiac uptake is Grade 2 or 3 on SPECT (Single Photon Emission Computed Exercise Tomography) utilizing one of the following radiotracers (1, 2, or 3):
    1) 99m technetium (Tc)-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD);
    2) 99mTc-labeled pyrophosphate (PYP);
    3) 99mTc-labeled hydroxymethylene diphosphonate (HMDP);
iii. Each of the following laboratory tests is negative for monoclonal protein (1, 2, and 3);
    1) Serum kappa/lambda free light chain ratio analysis;
    2) Serum protein immunofixation;
    3) Urine protein immunofixation;

5. Member has heart failure of New York Heart Association (NHYA) Class I, II, or III;
6. If member NYHA Class III heart failure, member does not have ATTR Amyloidosis Disease Stage 3 (defined as NT-proBNP > 3,000 ng/L and eGFR < 45 mL/min);
7. Member has one of the following (a or b):
    a. At least 1 prior hospitalization for heart failure;
    b. Current (within the last 30 days) clinical evidence of heart failure (e.g., exercise intolerance, unintentional weight loss, refractory volume overload, recurrent ventricular arrhythmias, hypotension and signs of inadequate perfusion [e.g., low, or narrowed pulse pressure, cool extremities, and mental status changes] see *Appendix D*);
8. Member has not had a liver transplant;
9. Amvuttra is not prescribed concurrently with Attruby™ or Onpattro®;
10. If member is currently receiving treatment with Vyndaqel®/Vyndamax™ and request is for concurrent use with Amvuttra (i.e., not switching from one agent to another), provider must submit evidence of both of the following (a and b):
    a. Member has experienced and maintained positive response to Vyndaqel/Vyndamax monotherapy following at least 6 months of monotherapy;
    b. Despite Vyndaqel/Vyndamax monotherapy, member continues to require cardiac-related hospitalization;
11. Dose does not exceed 25 mg every 3 months.

Approval duration: 12 months

C. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Hereditary Transthyretin-Mediated Amyloidosis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters: measures of polyneuropathy (e.g., motor strength, sensation, and reflexes), quality of life, motor

function, walking ability (e.g., as measured by timed 10-m walk test), and nutritional status (e.g., as evaluated by modified mass index);
3. Member has not had a prior liver transplant;
4. Amvuttra is not prescribed concurrently with Onpattro or Wainua;
5. If request is for a dose increase, new dose does not exceed 25 mg every 3 months.

Approval duration: 12 months

B. Transthyretin Amyloid Cardiomyopathy (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy, including but not limited to improvement or stabilization in any of the following parameters:
   a. Walking ability;
   b. Nutrition (e.g., body mass index);
   c. Cardiac related hospitalization;
   d. Cardiac procedures or laboratory tests (e.g., Holter monitoring, echocardiography, electrocardiogram, plasma BNP or NT-proBNP, serum troponin);
3. Amvuttra is not prescribed concurrently with Attruby or Onpattro;
4. If request is for a dose increase, new dose does not exceed 25 mg every 3 months.

Approval duration: 12 months

III. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

IV. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

V. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ATTR-CM: cardiomyopathy of transthyretin-mediated amyloidosis
eGFR: estimated glomerular filtration rate
FDA: Food and Drug AdministrationhATTR: hereditary transthyretin-mediated
NT-proBNP: N-terminal pro-B-type natriuretic peptide
RNA: ribonucleic acid
TTR: transthyretin

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- To confirm amyloidosis, the demonstration of amyloid deposits via tissue biopsy is essential. Deposition of amyloid in the tissue can be demonstrated by Congo red staining of biopsy specimens. With Congo red staining, amyloid deposits show a characteristic green birefringence under polarized light; however, negative biopsy results should not be interpreted as excluding the disease.
- DNA sequencing is usually required for genetic confirmation. Current techniques for performing sequence analysis of TTR, the only gene known to be associated with TTR amyloidosis, detect > 99% of disease-causing mutations.
- While signs and symptoms of advanced heart failure are variable, common manifestations of advanced hear failure include exercise intolerance, unintentional weight loss, refractory volume overload, recurrent ventricular arrhythmias, as well as hypotension and signs of inadequate perfusion (e.g., low, or narrowed pulse pressure, cool extremities, and mental status changes). Laboratory testing that may reveal signs of advanced heart failure includes indications of poor or worsening renal function, hyponatremia, hypoalbuminemia, congestive hepatopathy, elevated serum natriuretic peptide levels. Pulmonary edema, pleural effusions, and/or pulmonary vascular congestion on chest radiograph are also suggestive of advanced heart failure.

VI. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Polyneuropathy of hATTR, ATTR-CM	25 mg SC every three months	25 mg/3 months

VII. Product Availability
Single-dose prefilled syringe: 25 mg/0.5 mL

VIII. References
1. Amvuttra Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; March 2025. Available at: https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf. Accessed January 14, 2026.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). NCT03759379: HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis). Updated July 20, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03759379. Accessed July, 10, 2023.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). NCT04153149: HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy. Updated July 16, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04153149. Accessed July 29, 2021.

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5. Magrinelli F, Fabrizi GM, Santoro L, et al. Pharmacological treatment for familial amyloid polyneuropathy. Cochrane Database Syst Rev. 2020 Apr 20;4(4):CD012395.
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8. Alcantara, M., Mezei, M., Baker, S., et al. Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. Canadian Journal of Neurological Sciences 2022. 49 (1): 7-18.
9. 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.
10. Fontana M, Maurer MS, Gillmore JD, et al. Outpatient worsening heart failure in patients with transthyretin amyloidosis with cardiomyopathy in the HELIOS-B trial. J Am Coll Cardiol. 2025 Feb 25;85(7):753-761.
11. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2 - Evidence base and standardized methods of imaging. J Cardiac Failure; 2019: 24(11): e2-e39.
12. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2- Diagnostic criteria and appropriate utilization. Journal of Cardiac Failure; 2019: 25(11): 854-865.
13. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC, August 2019; 7(8): 709-16.
14. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023 Mar 21;81(11):1076-1126.
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Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0225	Injection, vutrisiran, 1 mg

Reviews, Revisions, and Approvals	Date
Policy created	04/2023
4Q 2023 annual review: no significant changes; references reviewed and updated.	10/2023
2Q 2024 annual review: added Wainua to list of drugs that should not be prescribed concurrently; references reviewed and updated.	04/2024
2Q 2025 annual review: RT4: added new indication for ATTR-CM per updated prescribing information.	04/2025
2Q 2026 annual review: for diagnosis by cardiac uptake, specified radionucleotide scan should be SPECT (Single Photon Emission Computed Exercise Tomography) per updated 2025 ACC Clinical Guidance; removed Tegsedi from criteria as agent is discontinued; revised initial approval duration from 6 to 12 months; references reviewed and updated.	04/2026