Clinical Policy: Vutrisiran (Amvuttra)

Reference Number: CP.PHAR.550
Effective Date: 06.13.22
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 amyloidosis (hATTR) in adults
- The cardiomyopathy of wild-type or hereditary ATTR (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations, and urgent heart failure visits.

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 health plans affiliated with Centene Corporation® that Amvuttra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

** See Section B below for transthyretin amyloid cardiomyopathy*

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. Biopsy is positive for amyloid deposits or 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, Tegsedi, or Wainua;
8. Dose does not exceed 25 mg every 3 months.

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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 a radionuclide scan 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 (i.e., signs and symptoms, 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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

** See Section B below for transthyretin amyloid cardiomyopathy*

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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, Tegsedi, or Wainua;
5. If request is for a dose increase, new dose does not exceed 25 mg every 3 months.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. 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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ATTR-CM: cardiomyopathy of transthyretin-mediated amyloidosis
eGFR: estimated glomerular filtration rate
FDA: Food and Drug Administration
hATTR: 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.

V. Dosage and Administration

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

VI. Product Availability

Single-dose prefilled syringe: 25 mg/0.5 mL

VII. 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 March 26, 2025.
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 29, 2021.
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.
4. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013 Feb 20;8:31.
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.

6. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2023 Mar; 30 (1): 1-9.
7. Obici L, Polydefkis M, Gonzalez-Duarte A, et al. HELIOS-A: 9-month results from the randomized treatment extension period of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy. Available at: https://capella.alnylam.com/wp-content/uploads/2023/05/HELIOS-A_9-Month-Results-from-the-Randomized-Treatment-Extension-Period-of-Vutrisiran-in-Patients-with-Hereditary-Transthyretin-Mediated-Amyloidosis-with-Polyneuropathy.pdf. Accessed February 12, 2024.
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.

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	P&T Approval Date
Policy created pre-emptively	08.10.21	11.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2022 annual review: RT4: converted PEPP to post-FDA-approved status; clarified Commercial approval duration is 6 months or members renewal date, whichever is longer; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	06.28.22	11.22
Updated HCPCS code: [J0225]	01.06.23	
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.10.23	11.23
2Q 2024 annual review: added Wainua to list of drugs that should not have been previously received or prescribed concurrently; references reviewed and updated.	02.12.24	05.24
2Q 2025 annual review: removed criteria "member has not received prior treatment with Onpattro, Tegsedi, or Wainua" per competitor analysis and to allow alternative therapy as a result of Tegsedi market withdrawal; references reviewed and updated. RT4: added new indication for ATTR-CM per updated prescribing information.	03.27.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or

regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.