| Reference number(s) |
| --- |
| 5499-A |

# Standard Medicare Part B Management Amvuttra

## Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

| Brand Name | Generic Name |
| --- | --- |
| Amvuttra | vutrisiran |

## Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

### FDA-approved Indications[1]

Amvuttra is indicated for the treatment of:

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

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

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| --- |
| 5499-A |

# Documentation

The following documentation must be available, upon request, for all submissions:

## Initial Requests

- For the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN):
  - Testing or analysis confirming a pathogenic variant in the TTR gene.
  - Medical record documentation demonstrating clinical manifestations of transthyretin-type familial amyloid polyneuropathy [ATTR-FAP] (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
  - Medical record documentation confirming the member demonstrates signs and symptoms of polyneuropathy.
- For the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM):
  - Chart notes or medical record documentation confirming history of prior hospitalization for heart failure or confirming the member demonstrates clinical symptoms of heart failure at baseline.
  - For biopsy-proven disease:
    - Tissue biopsy from cardiac or noncardiac sites confirming the presence of the transthyretin amyloid deposition.
    - Immunohistochemical analysis, mass spectrometry, tissue staining, or polarized light microscopy results confirming the presence of transthyretin precursor proteins.
  - For technetium-labeled bone scintigraphy proven disease:
    - Scintigraphy tracing results confirming the presence of amyloid deposits.
    - Serum kappa/lambda free light chain ratio, serum protein immunofixation, and urine protein immunofixation test results showing the absence of monoclonal proteins.
  - For hereditary ATTR-CM: testing or analysis confirming a pathogenic or likely pathogenic variant in the transthyretin (TTR) gene.

## Continuation Requests

- For the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN):
  - Chart notes or medical record documentation supporting clinical benefit of therapy compared to baseline (e.g., improvement of neuropathy severity and rate of disease progression as demonstrated by the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, polyneuropathy disability (PND) score, FAP disease stage, manual grip strength).

- For the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM):
    - Chart notes or medical record documentation supporting clinical benefit of therapy compared to baseline (e.g., improvement in rate of disease progression as demonstrated by distance walked on the 6-minute walk test, the Kansas City Cardiomyopathy Questionnaire–Overall Summary [KCCQ-OS] score, cardiovascular-related hospitalizations, New York Heart Association [NYHA] classification of heart failure, left ventricular stroke volume, N-terminal B-type natriuretic peptide [NT-proBNP] level).

# Coverage Criteria

## Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis[1-3]

Authorization of 12 months may be granted for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:

- Member is 18 years of age or older.
- The diagnosis is confirmed by detection of a pathogenic variant in the TTR gene.
- Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
- Member is not a liver transplant recipient.
- The requested medication will not be used in combination with patisiran (Onpattro), inotersen (Tegsedi), eplontersen (Wainua),acoramidis (Attruby), tafamidis meglumine (Vyndaqel), or tafamidis (Vyndamax).

## Cardiomyopathy of Wild-type or Hereditary Transthyretin-Mediated Amyloidosis[1,4-7]

Authorization of 12 months may be granted for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) when all of the following criteria are met:

- Member is 18 years of age or older.
- Member has medical history of heart failure with at least one prior hospitalization for heart failure (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker), OR exhibits clinical symptoms of heart failure (e.g., volume overload, dyspnea, fatigue, orthostatic hypotension, syncope, peripheral edema) at baseline.
- The diagnosis is confirmed by either of the following criteria:
    - Member meets both of the following criteria for biopsy proven disease:

        - Presence of transthyretin amyloid deposits on analysis of biopsy from cardiac or noncardiac sites.
        - Presence of transthyretin precursor proteins was confirmed by immunohistochemical analysis, mass spectrometry, tissue staining, or polarized light microscopy.
    - Member meets both of the following criteria for technetium-labeled bone scintigraphy proven disease:
        - Presence of amyloid deposits confirmed by technetium-labeled bone scintigraphy tracing.
        - Systemic light chain amyloidosis is ruled out by showing the absence of monoclonal proteins by all of the following tests: a) serum kappa/lambda free light chain ratio, b) serum protein immunofixation, and c) urine protein immunofixation.
- For members with hereditary ATTR-CM: the diagnosis is confirmed by detection of a pathogenic or likely pathogenic variant in the TTR gene.
- Member does not have prior or anticipated heart, liver, or other organ transplant or implantation of left-ventricular assist device.
- The requested medication will not be used in combination with patisiran (Onpattro), inotersen (Tegsedi), eplontersen (Wainua), acoramidis (Attruby), tafamidis meglumine (Vyndaqel), or tafamidis (Vyndamax). .

# Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- For the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN):
    - Member must have demonstrated a beneficial response to treatment with the requested medication compared to baseline (e.g., improvement of neuropathy severity and rate of disease progression as demonstrated by the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, polyneuropathy disability (PND) score, FAP disease stage, manual grip strength).
- For the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM):
    - Member must have demonstrated a beneficial response to treatment with the requested medication (e.g., improvement in rate of disease progression as demonstrated by

distance walked on the 6-minute walk test, the Kansas City Cardiomyopathy Questionnaire–Overall Summary [KCCQ-OS] score, cardiovascular-related hospitalizations, New York Heart Association [NYHA] classification of heart failure, left ventricular stroke volume, N-terminal B-type natriuretic peptide [NT-proBNP] level).

# Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Amvuttra
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- Guideline of transthyretin-related hereditary amyloidosis for clinicians.
- Hereditary Transthyretin Amyloidosis. In: GeneReviews.
- Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis.
- Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review.
- Transthyretin Amyloid Cardiomyopathy-Current and Future Therapies.
- Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Amvuttra are covered.

# Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the above initial criteria for hereditary transthyretin-mediated amyloidosis (hATTR-PN) can be found in a guideline from Ando and colleagues and a Gene Reviews chapter discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy shows amyloid deposits that bind to anti-TTR antibodies, and there is identification of pathogenic variants in the TTR gene.

The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers, and gene-silencing therapies (such as Amvuttra). Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

Support for using the above initial criteria for the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) can be found in an expert consensus recommendation from Maurer and colleagues. Diagnostic approaches for patients with suspected cardiac amyloidosis should include testing for monoclonal protein (using serum kappa/lambda free light chain ratio, serum protein immunofixation, or urine protein immunofixation tests) followed by scintigraphy or biopsy.

If monoclonal protein is detected, the patient cannot be diagnosed based on scintigraphy alone and performance of biopsy from a clinically affected organ (e.g., endomyocardial biopsy if the heart is affected), abdominal fat, or bone marrow is necessary to definitively diagnose ATTR-CM. Regardless of the site of biopsy, amyloid deposits must then undergo either immunofluorescence or mass spectrometry to confirm the amyloidosis subtype (light chain amyloidosis or ATTR). In patients with confirmed ATTR amyloidosis, TTR gene sequencing is necessary even if the patient does not have a family history of amyloidosis or evidence of polyneuropathy because the penetrance of hATTR varies among the variants and families.

Pharmacologic treatment approaches for TTR amyloidosis (ATTR) include ribonucleic acid (RNA)-targeted therapies (e.g., Amvuttra, Onpattro, Tegsedi, Wainua) that interfere with hepatic TTR synthesis, and transthyretin tetramer stabilizers (e.g., Vyndaqel, Vyndamax, Attruby) that reduce formation of TTR amyloid through stabilization of the tetramer configuration and subsequently prevent the release of amyloidogenic monomers. These therapies work to decrease TTR production. Currently, there is no literature supporting the combination use of Amvuttra with Onpattro, Tegsedi, Wainua, or Attruby.

# References

1. Amvuttra [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; March 2025.
2. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
3. Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2024 May 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed March 18, 2025.
4. Maurer MS, Sabahat B, Thibaud D, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075.
5. Ruberg FL, Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-2891.
6. Yadav JD, Othee H, Chan KA, et al. Transthyretin Amyloid Cardiomyopathy-Current and Future Therapies. Ann Pharmacother. 2021;55(12):1502-1514.
7. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134.