Corporate Medical Policy: Injectable Transthyretin-Mediated Amyloidosis (ATTR) Therapy **"Notification"** **POLICY EFFECTIVE OCTOBER 1, 2026**

Restricted Product(s):

- eplontersen (Wainua®) subcutaneous pre-filled syringe injection for administration by a healthcare professional
- patisiran (Onpattro®) intravenous infusion for administration by a healthcare professional
- vutrisiran (Amvuttra®) subcutaneous injection for administration by a healthcare professional

FDA Approved Use:

- Eplontersen (Wainua®)
  - For the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- Patisiran (Onpattro®)
  - For the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- Vutrisiran (Amvuttra®)
  - For the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
  - 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

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) [medical record documentation required]**; **AND**
   a. The request is for eplontersen (Wainua), patisiran (Onpattro), or vutrisiran (Amvuttra); **AND**
   b. The patient is 18 years of age or older; **AND**
   c. The diagnosis has been confirmed by BOTH of the following:
      i. Molecular genetic testing demonstrating a pathogenic or likely pathogenic variant in the transthyretin (*TTR*) gene **[medical record documentation required]**; **AND**
      ii. Confirmation of amyloid deposition by tissue biopsy, radionuclide cardiac scintigraphy with technetium-labeled bisphosphonates, and/or monoclonal antibody studies **[medical record documentation required]**; **AND**

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d. The patient has peripheral neuropathy associated with hATTR **[medical record documentation required]**; **AND**
    i. ONE of the following:
        1. A baseline polyneuropathy disability (PND) score of IIIb or lower **[medical record documentation required]**; **OR**
        2. A baseline Familial Amyloid Polyneuropathy (FAP) stage 1 or 2 **[medical record documentation required]**; **AND**
    ii. ONE of the following:
        1. Abnormal electrodiagnostic (nerve conduction) studies consistent with hATTR-associated polyneuropathy **[medical record documentation required]**; **OR**
        2. Abnormal neurological examination suggestive of neuropathy **[medical record documentation required]**; **AND**
    iii. The patient has presence of clinical manifestations of neuropathy prior to treatment initiation (e.g., sensory [e.g., neuropathic pain, altered and/or tingling sensation, numbness, impaired balance, etc.], motor [e.g., progressive weakness, walking difficulties, loss of dexterity, etc.], autonomic dysfunction [e.g., erectile dysfunction, lightheadedness/orthostatic hypotension/syncope/presyncope, genitourinary problems, GI manifestations, etc.]) **[medical record documentation required]**; **AND**
    iv. Other causes of peripheral neuropathy have been excluded **[medical record documentation required]**; **AND**
e. If the request is for eplontersen (Wainua), the pre-filled syringe is being requested; **AND**
f. If the request is for patisiran (Onpattro) or vutrisiran (Amvuttra), ONE of the following:
    i. The patient has tried and had an inadequate response to eplontersen (Wainua) **[medical record documentation required]**; **OR**
    ii. The patient has an intolerance or hypersensitivity to eplontersen (Wainua) **[medical record documentation required]**; **OR**
    iii. The patient has an FDA labeled contraindication to eplontersen (Wainua) **[medical record documentation required]**; **OR**
    iv. The patient is diagnosed with hATTR with a mixed phenotype, exhibiting both polyneuropathy and cardiomyopathy **[medical record documentation required]**; **OR**

2. The patient has a diagnosis of **cardiomyopathy of wild-type or hereditary (variant) transthyretin-mediated amyloidosis (ATTR-CM) [medical record documentation required]**; **AND**
    a. The request is for vutrisiran (Amvuttra); **AND**
    b. The patient is 18 years of age or older; **AND**
    c. The diagnosis has been confirmed by BOTH of the following:
        i. Molecular genetic testing demonstrating a pathogenic or likely pathogenic variant in the transthyretin (*TTR*) gene **[medical record documentation required]**; **OR**
        ii. Confirmation of amyloid deposition by tissue biopsy, radionuclide cardiac scintigraphy with technetium-labeled bisphosphonates, and/or monoclonal antibody studies **[medical record documentation required]**; **AND**
    d. The patient has clinical manifestations of cardiomyopathy (e.g., dyspnea, fatigue, orthostatic hypotension, syncope, peripheral edema) **[medical record documentation required]**; **AND**

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e. The patient has a history of heart failure (HF) with at least one prior hospitalization for HF or clinical evidence of HF (e.g., signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment) **[medical record documentation required]**; **AND**
f. The patient does NOT have NYHA Class IV HF, or NYHA Class III HF and considered high risk (e.g., N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) >3000 ng/L, estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2) **[medical record documentation required]**; **AND**
g. ONE of the following:
    i. The patient has tried and had an inadequate response to at least ONE of the following agents: acoramidis (Attruby), tafamidis (Vyndamax), OR tafamidis meglumine (Vyndaqel) **[medical record documentation required]**; **OR**
    ii. The patient has an intolerance or hypersensitivity to ONE of the following agents: acoramidis (Attruby), tafamidis (Vyndamax), OR tafamidis meglumine (Vyndaqel) **[medical record documentation required]**; **OR**
    iii. The patient has an FDA labeled contraindication to ALL of the following agents: acoramidis (Attruby), tafamidis (Vyndamax), AND tafamidis meglumine (Vyndaqel) **[medical record documentation required]**; **OR**
    iv. The patient is diagnosed with hATTR with a mixed phenotype, exhibiting both polyneuropathy and cardiomyopathy **[medical record documentation required]**; **AND**

3. The patient does NOT have amyloid light chain (AL) amyloidosis **[medical record documentation required]**; **AND**
4. The patient has NOT had prior liver transplantation or anticipated liver transplantation **[medical record documentation required]**; **AND**
5. The patient will NOT receive the requested agent in combination with any other TTR-directed therapy (e.g., acoramidis [Attruby], eplontersen [Wainua], patisiran [Onpattro], tafamidis [Vyndamax], tafamidis meglumine [Vyndaqel], vutrisiran [Amvuttra], etc.) **[medical record documentation required]**; **AND**
6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist, specialist in the treatment of amyloidosis) or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
7. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
8. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**

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3. The patient has a diagnosis of **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) [medical record documentation required]**; **AND**
    a. The request is for eplontersen (Wainua), patisiran (Onpattro), or vutrisiran (Amvuttra); **AND**
    b. ONE of the following:
        i. The patient continues to have a PND score of IIIb or lower **[medical record documentation required]**; **OR**
        ii. The patient continues to have FAP stage 1 or 2 **[medical record documentation required]**; **AND**
    c. The patient has demonstrated a positive clinical response (e.g., improved neurologic impairment, motor function, quality of life, and/or ambulation) while using the requested agent **[medical record documentation required]**; **AND**
    d. If the request is for eplontersen (Wainua), the pre-filled syringe is being requested; **OR**
4. The patient has a diagnosis of **cardiomyopathy of wild-type or hereditary (variant) transthyretin-mediated amyloidosis (ATTR-CM) [medical record documentation required]**; **AND**
    a. The request is for vutrisiran (Amvuttra); **AND**
    b. The patient has demonstrated a positive clinical response (e.g., reduction in cardiovascular events [e.g., hospitalizations for cardiovascular causes or urgent visits for heart failure], improvement or stabilization in the 6-Minute Walk Test [6MWT], reduction in heart failure symptoms) while using the requested agent **[medical record documentation required]**; **AND**
5. The patient will NOT receive the requested agent in combination with any other TTR-directed therapy (e.g., acoramidis [Attruby], eplontersen [Wainua], patisiran [Onpattro], tafamidis [Vyndamax], tafamidis meglumine [Vyndaqel], vutrisiran [Amvuttra], etc.) **[medical record documentation required]**; **AND**
6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist, specialist in the treatment of amyloidosis) or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
7. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
9. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

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FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
eplontersen (Wainua®) subcutaneous (SC) injection pre-filled syringe	hATTR-PN in patients ≥18 years old	SC: 45 mg once monthly	C9399** J3490** J3590**	540
patisiran (Onpattro®) intravenous (IV) infusion	Polyneuropathy of hATTR in patients ≥18 years old	IV: • Patients weighing <100 kg: 0.3 mg/kg once every 3 weeks • Patients weighing ≥100 kg: 30 mg once every 3 weeks	J0222	5,400
vutrisiran (Amvuttra®) subcutaneous (SC) injection	Polyneuropathy of hATTR in patients ≥18 years old Cardiomyopathy of ATTR in patients ≥18 years old	SC: 25 mg once every 3 months	J0225	100

***Maximum units allowed for duration of approval**
****Non-specific assigned HCPCS codes, must submit requested product NDC**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:

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a. History of a severe adverse event following the injection or infusion of the requested medication (i.e., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure); **OR**
b. Conditions that cause an increased risk for severe adverse event (i.e., unstable renal function, cardiopulmonary conditions, unstable vascular access); **OR**
c. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
d. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
e. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
f. Re-initiation of therapy, defined as ONE of the following:
    i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
    ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
g. Requirement of a change in the requested restricted product formulation; **AND**

3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

1. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21.
2. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. *BMC Neurol*. 2017;17(1):181.
3. Adams D, Tournev IL, Taylor MS, et al. HELIOS-A Collaborators. 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.
4. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
5. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018 Jul 5;379(1):22-31.
6. Coelho T, Marques W Jr, Dasgupta NR, et al. NEURO-TTRansform Investigators. Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. *JAMA*. 2023 Oct 17;330(15):1448-1458.
7. Fontana M, Berk JL, Gillmore JD, et al. HELIOS-B Trial Investigators. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025 Jan 2;392(1):33-44.

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8. Karam C, Mauermann ML, Gonzalez-Duarte A, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts. *Muscle & Nerve*. 2024;69(3):273-287.
9. Kittleson M, Ruberg F, Ambardekar A, 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. *JACC.* 2023 Mar;81(11):1076-1126.
10. Luigetti M, Romano A, DiPaolantonio A, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: Current perspectives on improving patient care. *Ther Clin Risk Manag*. 2020;16:109–123. Published online 2020 Feb 21.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q4 annually.

October 2026: Original medical policy criteria issued. Consolidated “Eplontersen (Wainua)”, “Patisiran (Onpattro)”, and “Vutrisiran (Amvuttra)” medical policies into the following “Injectable Transthyretin-Mediated Amyloidosis (ATTR) Therapy” medical policy. Reformatted diagnostic criteria for hATTR-PN and ATTR-CM indications to require both genetic confirmation and confirmed amyloid deposition. Reformatted confirmation of peripheral neuropathy for hATTR-PN indication to include either abnormal electrodiagnostic studies consistent with hATTR-associated polyneuropathy or abnormal neurological examination suggestive of neuropathy, and presence of clinical manifestations of neuropathy. Added requirement that the patient does not have AL amyloidosis. Removed Tegsedi from list of TTR-directed therapies not to be used in combination due to market withdrawal. Adjusted maximum units for Wainua for clarity according to FDA labeled dosing. **Policy notification given 8/3/2026 for effective date 10/1/2026**.
*Further historical criteria changes and updates for Corporate Medical Policies for each individual drug are available upon request from Medical Policy and/or Corporate Pharmacy.

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