POLICY: Amyloidosis – Onpattro Utilization Management Medical Policy
- Onpattro® (patisiran intravenous infusion – Alnylam)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 12/10/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Onpattro, a lipid nanoparticle formulated RNA interference therapeutic, is indicated for treatment of adults with **polyneuropathy of hereditary amyloid transthyretin amyloidosis (hATTR)**.[1] hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensorimotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Clinical Efficacy

The pivotal trial for Onpattro did not include patients with liver transplantation, which has historically been a treatment modality for hATTR.[1,6] A Phase IIIb, open-label trial evaluated the efficacy of Onpattro in adults with hATTR polyneuropathy progression post liver transplant (n = 23).[6] Patients received Onpattro at the FDA-approved dose for 12 months. The average of Month 6 and Month 12 serum TTR reduction was 91%. In addition, improvements in neuropathy, quality of life, autonomic symptoms from baseline to Month 12, and stabilized disability and nutritional status were noted. The prescribing information for Onpattro notes that age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of Onpattro or TTR reduction.[1]

APOLLO-B was a Phase III, double-blind, trial that randomized patients with hATTR cardiac amyloidosis to receive Onpattro or placebo for 12 months (n = 360).[7] The primary endpoint was a change from baseline in the distance walked on 6-minute walk test. The first secondary endpoint was the change from baseline to Month 12 in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score. A composite of death from any cause, cardiovascular events, and change from baseline in the 6-minute walk test distance over 12 months, was a secondary endpoint. A third secondary endpoint assessed the composite of death from any cause, hospitalization for any cause, and urgent heart failure visits. At Month 12, the magnitude of decline in 6-minute walk distance was significantly lower in the Onpattro group (-8.15 meters) vs. placebo (-21.35 meters) [median difference 14.69 meters; 95% confidence interval [CI]: 0.69, 28.69; P = 0.02). The KCCQ-OS score was slightly improved with Onpattro (+0.3 points), but reduced with placebo (-3.4 points), leading to a statistically significant between group difference (3.7 points; 95% CI: 0.2, 7.2; P = 0.04). The secondary composite endpoints were not significant between groups. Based on these findings, the FDA cited insufficient evidence of clinical meaningfulness for the treatment of cardiomyopathy of hATTR and issued a complete response letter to the manufacturer of Onpattro for the treatment of cardiomyopathy of hATTR.[8]

Guidelines

A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR

polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Onpattro for polyneuropathy of hATTR; but, it is noted that the product is not indicated for cardiomyopathy of hATTR amyloidosis (APOLLO-B trial results are acknowledged).[9] In general, Onpattro and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax™ (tafamidis capsules)/Vyndaqel® (tafamidis meglumine capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of ATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Onpattro. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Onpattro as well as the monitoring required for adverse events and long-term efficacy, approval requires Onpattro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin pathogenic variant as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a history of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

Dosing. Approve the following dosing (A and B):
A) The dose is up to 0.3 mg/kg given intravenously up to a maximum dose of 30 mg; AND
B) The dose is administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onpattro is not recommended in the following situations:

1. **Concurrent use with other medications indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy (e.g., Amvuttra [vutrisiran subcutaneous injection], Attruby [acoramidis tablets], Tegsedi [inotersen subcutaneous injection], Wainua [eplontersen subcutaneous injection], or a tafamidis product.)**
   The requested medication should not be administered in combination with other medications indicated for polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy. Combination therapy is generally not recommended due to a lack of controlled clinical trial data supporting additive efficacy.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Onpattro® [prescribing information]. Cambridge, MA: Alnylam; January 2023.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
5. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.
6. Schmidt HH, Wixner J, Plante-Bordeneuve V; on behalf of the Patisiran Post-LT Study Group. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. *Am J Transplant.* 2022;22:1646-1657.
7. Maurer MS, Kale P, Fontanta M, et al; for the APOLLO-B Trial Investigators. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med.* 2023;389(17); 1553-1565.
8. Alnylam announces receipt of complete response letter from U.S. FDA for supplemental new drug application for patisiran for the treatment of the cardiomyopathy of ATTR amyloidosis [press release]. Cambridge, MA: Alnylam; October 6, 2023. Available at: https://investors.alnylam.com/press-release?id=27741. Accessed on: December 1, 2025.
9. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC*. 2023;81(11):1076-1126.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** The criterion requiring the patient did not have a history of liver transplantation was removed.	11/30/2022
Annual Revision	No criteria changes.	11/29/2023
Selected Revision	Conditions Not Recommended for Approval **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection) or a Tafamidis Product.** Wainua was added to this condition not recommended for approval.	01/03/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR)**: For diagnosis confirmed by genetic testing, rephrased the term "mutation" to "pathogenic variant". **Conditions Not Recommended for Approval:** Concurrent use with other medications indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy (e.g., Amvuttra (vutrisiran subcutaneous injection), Attruby (acoramidis tablets), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.) was changed to as listed (previously, concomitant use with Amvuttra [vutrisiran subcutaneous injection], Tegsedi [inotersen subcutaneous injection], Wainua [eplontersen subcutaneous injection], or a Tafamidis product was listed.)	12/04/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** The patient does not have a history of liver transplant was added as an approval requirement.	12/10/2025