Drug Coverage Policy

Effective Date 3/1/2025
Coverage Policy Number.....IP0418
Policy Title.....Onpattro

Amyloidosis – Onpattro

- Onpattro® (patisiran intravenous infusion – Alnylam)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

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 sensiomotor 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.

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, genetic test results, claims records, and/or other information.

Onpattro is considered medically necessary when the following criteria are met: 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, and D):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Documentation provided that the patient has a transthyretin pathogenic variant as confirmed by genetic testing; AND
   - **C)** Documentation provided that the 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)** 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.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0222	Injection, patisiran, 0.1 mg

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 3, 2024.
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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	**Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** **Removed** 'Documentation that other causes of neuropathy have been excluded (for example, diabetes)' **Updated** 'Documented diagnosis of hereditary transthyretin-mediated (hATTR) amyloidosis confirmed by a transthyretin *(TTR)* genetic variant (pathogenic or likely pathogenic variant)' to 'Patient has a transthyretin pathogenic variant as confirmed by genetic testing'	10/1/2024

	Updated 'Documentation of symptomatic polyneuropathy confirmed by history and clinical exam, electromyography, or nerve conduction velocity' to 'Patient has symptomatic polyneuropathy; 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.' **Conditions Not Covered.** **Removed** (1) Treatment of Cardiomyopathy hATTR in the Absence of Polyneuropathy Symptoms, (2) Treatment of Polyneuropathy Not Related to hATTR Amyloidosis. **Conditions Not Covered.** **Removed** (1) Treatment of Cardiomyopathy hATTR in the Absence of Polyneuropathy Symptoms, (2) Treatment of Polyneuropathy Not Related to hATTR Amyloidosis.	
Annual Revision	**Added "Documentation**: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, genetic test results, claims records, and/or other information." **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR)** **Updated** criteria **from** "Patient has a transthyretin pathogenic variant as confirmed by genetic testing" **to** "Documentation provided that the patient has a transthyretin pathogenic variant as confirmed by genetic testing." **Updated** criteria **from** "Patient has symptomatic polyneuropathy" **to** "Documentation provided that the patient has symptomatic polyneuropathy." **Conditions Not Covered** 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	3/1/2025

	[eplontersen subcutaneous injection], or a Tafamidis product was listed.)	

The policy effective date is in force until updated or retired.