Medical benefit drug policies are a source for WyoBlue Advantage medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 06/06/2025

Onpattro® (patisiran)

HCPCS: J0222

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy (formerly known as familial amyloid polyneuropathy, or FAP)
      i. Signs and symptoms of ocular or cerebral area involvement (such as in ocular amyloidosis or primary/leptomeningeal amyloidosis), if present, must not predominate over polyneuropathy symptomology associated with hATTR
   c. Documentation of TTR gene mutation
   d. Documentation of clinical signs and symptoms of peripheral neuropathy (such as: tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking)
      AND/OR
      Documentation of clinical signs and symptoms of autonomic neuropathy symptoms (such as: orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety])
   e. Must have a baseline polyneuropathy disability (PND) score ≤ IIIb and/or baseline FAP Stage 1 or 2
   f. Onpattro will not be used in combination with other therapies approved for transthyretin-mediated amyloidosis
   g. Must not have New York Heart Association (NYHA) heart failure classification >2
   h. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in WyoBlue Advantage's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit.

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center

This policy and any information contained herein is the property of WyoBlue Advantage and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and WyoBlue Advantage employees for the purpose of coverage determinations.

for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Transthyretin amyloidosis (ATTR) is a progressive, life-threatening disorder characterized by the deposition of amyloid fibrils composed of transthyretin (TTR), a plasma transport protein for thyroxine and vitamin A that is predominantly produced by the liver and to a lesser extent by the choroid plexus and in retinal cells.

- In ATTR, TTR misfolds, causing it to aggregate into amyloid fibrils that accumulate in organs, nerves, and tissues. The buildup of these amyloid deposits results in progressive dysfunction at the site of deposition. Amyloid deposition can occur in the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral nervous system, and central nervous system. The phenotype is driven by deposition site and may be predominantly cardiac, neurologic, or mixed.

- There are two types of ATTR: hereditary (hATTR), or variant, which is due to inherited mutations of the TTR gene that cause misfolding of the tetramer subunits, and wild-type, which occurs in the presence of a normal TTR gene, is typically associated with aging, and is most often diagnosed in men 65 years and older. In wild-type ATTR, TTR typically only deposits in the heart and manifests as cardiac symptoms. hATTR, in contrast, may be predominantly neuropathic, cardiomyopathy, or a mixed phenotype characterized by both

- ATTR is the most common form of hereditary amyloidosis. Approximately 120 different mutations or gene deletions have been identified in the TTR gene, with Val30Met as the most prevalent in the world.

- hATTR with polyneuropathy (hATTR-PN) is the most common neurologic manifestation. Without treatment, patients will have progressive neuropathy and disability ultimately resulting in death within 10-15 years of disease onset.

- Patients with hATTR-PN may present with peripheral neuropathy (sensory and motor; tingling or increased pain in the hands, feet and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy (e.g., orthostasis, abnormal sweating, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety]), GI impairment, cardiomyopathy, nephropathy, or ocular deposition. Most hATTR-PN cases, however, are classified as neuropathic.

- Amyloid deposition induces a length-dependent peripheral neuropathy beginning in the lower limbs with symptoms like toe discomfort due to numbness and spontaneous pain. Continued aggregation of amyloid on the nerve fibers contributes to sensory loss extending upwards toward the proximal lower limbs as motor deficits and impaired sensations occur. Walking becomes increasingly difficult as balance and gait are affected. Neuropathic pain transitions to a burning sensation worsening at night. Over time, sensory deficit extends to the upper limbs, forearms, fingers and trunk and motor deficit follows with the same length dependent progression. At this stage, potentially life-threatening autonomic dysfunction is present manifesting as orthostatic hypotension, anhidrosis, neurogenic bladder, disturbances of gastrointestinal motility, and sexual impotence.

- Cardiac disease may occur in approximately 50% of patients with hATTR-PN. Ocular involvement is also common, including vitreous opacity, dry eye, glaucoma, and pupillary disorder.

- A rarer presentation of hATTR is leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity (oculoleptomeningeal amyloidosis). A number of mutations have reportedly been linked to this type of hATTR, though it may also manifest in more advanced cases of Val30MET hATTR-PN.

This policy and any information contained herein is the property of WyoBlue Advantage and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and WyoBlue Advantage employees for the purpose of coverage determinations.

  - Central nervous system symptoms include stroke, subarachnoid hemorrhage, dementia, ataxia, seizures, and sensorineural hearing loss.

  - The source of mutant TTR in (oculo)leptomeningeal and meningovascular amyloidosis is thought to be the choroid plexus and retinal cells versus the liver. As such, ocular and meningovascular manifestations are commonly seen after liver transplantation because the source of mutant TTR is left unaffected.

  - To date, no treatments have been proven to be beneficial for the treatment of (oculo)leptomeningeal and meningovascular amyloidosis.

- The 2013 guideline of transthyretin-related hereditary amyloidosis for clinicians recommends that the most reliable diagnostic approach involves genetic testing and tissue biopsy to confirm the presence of active amyloid formation. Genetic testing is needed to document the TTR gene mutations; if testing is normal, a diagnosis of hATTR is excluded.

- Options for treatment of hATTR are limited. Treatment strategies for hATTR include depletion of the source of mutant TTR, inhibiting TTR formation, stabilizing the TTR molecule from dissociating, and therapy directed at removing the amyloid deposits. Regardless of the choice of treatment, the 2013 guidelines and expert opinion from a panel of experts (2024) recommend initiation as soon as possible after diagnosis to slow or halt disease progression. The best outcomes have been shown in patients diagnosed at younger ages and/or without advanced disease.

- For hATTR-PN, our best treatment option historically had been orthoptic liver transplant, which removes the source of mutant TTR and was considered the gold standard for hATTR-PN treatment early in the course of disease. In hATTR-PN, the liver is the primary source of mutant TTR; transplantation eliminates approximately 95% of the production of mutant TTR and may slow or halt disease progression outside of the brain and/or eyes, though nerve function rarely improves post-transplant. Transplant does not effectively prevent cardiomyopathy, however, and is not recommended for patients with late stage hATTR-PN or leptomeningeal disease. With later stages of hATTR-PN and cardiomyopathy, there are concerns of disease progression due to deposition of wild-type TTR from the transplanted liver on the preexisting amyloid from the variant TTR.

- Numerous disease-modifying therapeutics are now available for hATTR-PN, including Amvuttra (vutrisiran), Onpattro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpattro, and Wainua specifically; however, they do note that early detection is critical and patients with early-stage disease should be treated with any approved drugs as they become available and as the patient's disease state meets drug indications, independent of liver transplant plans.

- Amvuttra, Onpattro, and Wainua are FDA-approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Of these products, only Wainua is FDA approved to be administered by the patient or caregiver; a healthcare provider is required for administration of Amvuttra and Onpattro per the approved labeling. To date, there is no literature supporting the use of one product over another, nor is there support for the use of any of these products together or in combination with other therapies approved for ATTR (e.g., tafamidis [Vyndamax® and Vyndaqel®], acoramidis [Attruby®]). The 2024 expert opinion does not offer recommendations on choice of specific treatment due to the lack of direct comparison trials and advises that clinicians consider the efficacy and safety considerations, in addition to any comorbidities and personal preferences around ease of use for an individual patient.

- Onpattro is a small interfering ribonucleic acid agent (siRNA) targeting TTR. It works by silencing a portion of RNA involved in causing the disease. Onpattro is designed to deliver the drug directly into the liver to interfere with RNA production of an abnormal form of TTR. By preventing this, the drug can help reduce the accumulation of amyloid deposits in peripheral nerves.

This policy and any information contained herein is the property of WyoBlue Advantage and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and WyoBlue Advantage employees for the purpose of coverage determinations.

- In the pivotal phase 3 APOLLO trial, Onpattro demonstrated better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to those receiving the placebo infusions. Onpattro-treated patients also scored better on assessments of walking, nutritional status and the ability to perform activities of daily living.

- In clinical trials, Onpattro was only evaluated in patients with a baseline polyneuropathy disability (PND) score ≤IIIb, which equates to a familial amyloidotic polyneuropathy (FAP) stage of 1 or 2. The PND score (range 0-IV) stages disease based on walking ability, while the FAP stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy. Onpattro was not evaluated in patients with baseline PND score of IV which, like FAP stage 3, designates patients with late-stage, significantly advanced disease who are wheelchair-bound or bedridden, therefore clinical trials do not support use in this patient population with advanced disease.

- Patients with a history of liver transplant were also excluded from clinical trials of Onpattro. There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Onpattro as they would not be expected to produce mutated TTR post-transplant.

- Additionally, there are no published clinical trials evaluating safety or efficacy of Onpattro for the treatment of any condition other than polyneuropathy of hATTR, and data is limited on the effect of Onpattro on other end organ dysfunction related to the underlying amyloidosis (i.e. cardiovascular outcomes).

References:

1. ONPATTRO™(patisiran) [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; February 2020.
2. Onpattro (patisiran) New Drug Review. IPD analytics. August 2018.
3. In first, FDA approved RNA interference drug from Alnylam. Available at: https://www.biopharmadive.com/news/alnylam-onpattro-patisiran-approval-fda-rna-interference/529700/. Accessed September 2018.
4. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transtyretin Amyloidosis. N Engl J Med. 2018;379(1):11-21. doi: 10.1056/NEJMoa1716153.
5. Adams D. Gonzalez-Duarte A, O'Riordan WD, et al. Supplement to: 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. doi: 10.1056/NEJMoa1716153.
6. 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 Neurology. 2017;17(1):181. doi: 10.1186/s12883-017-0948-5.
7. Sekijima Y, Yoshida K, Tokudo T, et al. Familial Transthyretin Amyloidosis. Gene Reviews [internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed September 2018.
8. ESI Express Scripts® Drug Evaluation: patisiran (Onpattro™) [Alnylam Pharmaceuticals, INC.] August 2018.
9. Tafamidis for transthyretin amyloid cardiomyopathy. National Institute for Health Research [internet]. Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/06/5124-Tafamidis-for-TTR-CM-V1.0-JUN2018-NON-CONF.pdfhttp://www.io.nihr.ac.uk/wp-content/uploads/2018/06/5124-Tafamidis-for-TTR-CM-V1.0-JUN2018-NON-CONF.pdf. Accessed: September 2018
10. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases. 2013;8:31. Doi: 10.1186?1750-1172-8-31.
11. Amvuttra (prescribing information). Cambridge, MA: Alnylam Pharmaceuticals, Inc.; June 2022.
12. Karam C, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts. Muscle Nerve. 2024 Mar;69(3):273-287. doi: 10.1002/mus.28026. Epub 2024 Jan 4. PMID: 38174864.

This policy and any information contained herein is the property of WyoBlue Advantage and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and WyoBlue Advantage employees for the purpose of coverage determinations.

Policy History		
#	Date	Change Description
1.0	Initial Effective Date: 01/01/2026	New policy

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

This policy and any information contained herein is the property of WyoBlue Advantage and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and WyoBlue Advantage employees for the purpose of coverage determinations.