



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN 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.

Effective Date: 08/08/2024

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. Must have diagnosis of peripheral nerve disease caused by hereditary transthyretin amyloidosis (hATTR; formerly known as familial amyloidosis polyneuropathy or FAP) with documented TTR mutation
 - 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 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])
 - d. Must have a baseline polyneuropathy disability (PND) score \leq IIIb and/or a baseline FAP Stage 1 or 2
 - e. Onpattro will not be used in combination with other therapies approved for transthyretin-mediated amyloidosis
 - f. No prior liver transplant
 - g. Must not have New York Heart Association heart failure classification >2
 - h. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN'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.

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

***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 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, 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, transthyretin dissociates its form then 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.
- ATTR is the most common form of hereditary amyloidosis and is caused by mutations in the TTR gene that are responsible for destabilization of the transthyretin protein. Hereditary transthyretin amyloidosis (hATTR) has an autosomal dominant inheritance pattern with variable penetrance; the phenotypic presentation of the disease varies across genotypes, geographic locations, and individuals. Approximately 120 different mutations or gene deletions have been identified in the TTR gene, with Val30Met as the most prevalent in the world.
- hATTR is a multisystem disease involving the heart, gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral and central nervous system. Depending on the mutation, the phenotype may be predominantly cardiac, neurologic, or mixed.
- 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.

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

- hATTR may also have a strictly cardiologic presentation with cardiomyopathy (hATTR-CM) where left ventricle ejection fraction is normal or only mildly reduced coupled with ventricular hypertrophy. Amyloid deposition commonly affects the conduction system as well, leading to bundle branch block and on occasion atrioventricular and sinoatrial block. ATTR with a predominantly cardiomyopathy phenotype may also occur sporadically sans inheritance pattern due to wild-type TTR.
- 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.
 - 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 the formation of TTR, stabilizing the TTR molecule from dissociating, and therapy directed at removing the amyloid deposits. For hATTR-PN, our best treatment option historically had been liver transplantation; however numerous disease-modifying therapeutics are now available including Amvuttra® (vutrisiran), Onpatro (patisiran), Tegsedi® (inotersen), and Wainua® (eplontersen).
- Regardless 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. Though the guidelines have not yet been updated to include Amvuttra, Onpatro, Tegsedi, and Wainua specifically, 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.
- Orthoptic liver transplant removes the source of mutant TTR and has been 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.
- Amvuttra, Onpatro, Tegsedi, and Wainua are approved by the FDA for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Of these products, only Wainua and Tegsedi are FDA approved to be administered by the patient or caregiver; a healthcare provider is required for administration of Amvuttra and Onpatro 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®)). 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.
- 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 \leq 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 Transthyretin 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->

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

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. Tegsedi (inotersen) [prescribing information]. Boston, MA: Akcea Therapeutics Inc; July 2020.
12. Amvuttra (prescribing information). Cambridge, MA: Alnylam Pharmaceuticals, Inc.; June 2022.
13. 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.

Policy History												
#	Date	Change Description										
1.8	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made										
1.7	Effective Date: 08/10/2023	Annual review of criteria was performed, no changes were made										
1.6	Effective Date: 08/04/2022	Removed FDA approved indications criteria and updated bullet e to prevent combination use with any drug approved for ATTR										
1.5	Effective Date: 10/07/2021	Annual review of criteria was performed, no changes were made.										
1.4	Effective Date: 10/08/2020	Policy update; Addition of trial and failure of preferred language to criteria (bullet j)										
1.3	Effective Date: 11/07/2019	Annual Review of Medical Policy										
1.2	Effective Date: 02/01/2019	UM medical management system update for BCNA and MAPPO <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
BCN	Yes											
MAPPO	Yes											
BCNA	Yes											
1.1	Effective Date: 12/01/2018	UM medical management system update for BCBS <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
BCN	Yes											
MAPPO	No											
BCNA	No											
1.0	Effective Date: 11/01/2018	New Drug Policy <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	No
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	No											
BCN	Yes											
MAPPO	No											
BCNA	No											

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

** 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>.*