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P&T Date: 06/05/2025

Wainua™ (eplontersen)

HCPCS: J3490

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 FAP or Coutinho Stage 1 or 2
 - f. Wainua 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 prior authorization and step therapy documents
- 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 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:

- 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.
 - 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), Onpatro® (patisiran), and Wainua® (eplontersen). Guidelines have not yet been updated to include Amvuttra, Onpatro, 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, Onpatro, 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 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®], 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.
- Wainua is a ligand-conjugated antisense oligonucleotide (LICA) directed at TTR. It works by binding to and degrading TTR messenger RNA (mRNA) in the liver to prevent the production of TTR protein. Preventing TTR protein synthesis in the liver can help reduce the accumulation of amyloid deposits in peripheral nerves. Wainua works most similarly to Tegsedi, though it is thought to be engineered to be better at entering the liver which is the primary source of TTR.
 - In the pivotal Phase III NEURO-TTRansform trial, patients treated with Wainua demonstrated consistent and sustained benefit on co-primary endpoints of serum TTR concentration and neuropathy impairment

measured by the modified Neuropathy Impairment Score +7 (mNIS+7), and key secondary endpoint of quality of life (QoL) on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN). The benefit of Wainua was demonstrated across the spectrum of hATTR-PN at 35, 66, and 85 weeks.

- In clinical trials, Wainua was only evaluated in patients with a baseline familial amyloid polyneuropathy (FAP) or Coutinho stage of 1 or 2. The FAP or Coutinho stage (stage 0-3) assesses the patient's level of ambulation and the severity/progression of neuropathy; stage 1 signifies ambulatory without assistance, and stage 2 is ambulatory with assistance. Wainua was not evaluated in patients with baseline FAP or Coutinho stage 3, which 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.
 - The Polyneuropathy disability (PND) scoring system may also be used to classify hATTR-PN progression. This score focuses on the patient's walking ability, and scores range from 0 – IV. A PND score <IIIb equates to a FAP or Coutinho stage of 1 or 2, and a PND score of IV is considered equivalent to FAP or Coutinho stage 3.
- Patients who were receiving treatment with any approved drug for hATTR or off-label use of diflunisal or doxycycline, and those who had been previously treated with Onpattro or other oligonucleotide or RNA therapeutics were excluded from the clinical trial, as were those with a history of liver transplant or NYHA functional classification of ≥ 3 . There is no literature to support that patients who received a liver transplant would experience benefit from treatment with Wainua as they would not be expected to produce mutated TTR post-transplant.
- Additionally, there are no published clinical trials evaluating safety or efficacy of Wainua for the treatment of any condition other than hATTR-PN, and data is limited at this time on the effect of Wainua on other end organ dysfunction related to the underlying amyloidosis (i.e., cardiovascular outcomes).

References:

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4. IPD Analytics. Payer & Provider Insights. December 2023. Accessed December 27, 2023. <https://www.ipdanalytics.com>.
5. IPD Analytics. The Evolving Treatment Paradigm of Transthyretin-Related Amyloidosis. November 2021. Accessed February 21, 2022. <https://www.ipdanalytics.com>
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7. 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
1.0	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>.*