Original Effective Date: 06/27/2024
Current Effective Date: 09/01/2024
Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
Policy Number: C27703-A

Wainua (eplontersen)

PRODUCTS AFFECTED

Wainua (eplontersen)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):
   1. Documented diagnosis of hereditary transthyretin-mediated amyloidosis associated polyneuropathy (hATTR-PN)

AND

2. Documentation of BOTH of the following [DOCUMENTATION REQUIRED]:
   (a) Pathogenic transthyretin (TTR) mutation verified by genetic testing
   NOTE: More than 120 different transthyretin (TTR) gene mutations have been identified, with predominant symptom presentation varying by genotype. The most common mutations in the US are V122I, T60A, and V30M
   AND
   (b) ONE of the following: Polyneuropathy disability (PND) score ≤ IIIb, Familial amyloidotic polyneuropathy (FAP) stage 1 or 2, OR Neuropathy impairment score (NIS) between 10 and 130

   AND
3. Documentation of presence of clinical signs and symptoms of the disease such as: Peripheral sensory-motor neuropathy (e.g., neuropathic pain, paresthesia, weakness, bilateral carpal tunnel syndrome, difficulty walking), Autonomic neuropathy (e.g., hypotension, recurrent urinary tract infections, sexual dysfunction, sweating abnormalities, urinary retention), Gastrointestinal manifestations (e.g., diarrhea, nausea, vomiting, unintentional weight loss), Cardiovascular manifestations (e.g., arrhythmias, conduction abnormalities, heart failure)
   AND
4. Documentation the member has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product (e.g., gabapentin, pregabalin) or a tricyclic antidepressant (e.g., amitriptyline, nortriptyline), or Serotonin/Norepinephrine Reuptake Inhibitors (e.g., duloxetine)
   AND
5. Prescriber attests member will not receive Wainua in combination with another TTR-lowering agent, including Amvuttra, Tegsedi, Onpattro OR TTR-stabilizing agent, including diflunisal, Vyndaqel, Vyndamax
   AND
6. Prescriber attestation that member has been counseled on need for Vitamin A supplementation during therapy
   MOLINA REVIEWER: See Other Special Considerations for additional information.

CONTINUATION OF THERAPY:

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):
   1. Documentation of a positive response to therapy (e.g., improved neurologic impairment, motor function, slowing of disease progression, cardiac parameters, improvement in baseline scores: Polyneuropathy disability (PND) score ≤ IIIb OR FAP Stage 1 or 2, neuropathy impairment score) [DOCUMENTATION REQUIRED]
      AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:
45 mg once monthly

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Antisense Oligonucleotide (ASO) Inhibitor Agents

FDA-APPROVED USES:
Indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare condition affecting about 50,000people worldwide caused by a genetic mutation in the transthyretin (TTR) gene. Mutations in the TTR gene lead to de-stabilization, misfolding and aggregation into insoluble amyloid fibrils which deposit into multiple sites such as the nervous system, heart, kidneys, and eyes. There are multiple TTR mutations, the most prevalent being TTR V30M. Common symptoms of hATTR amyloidosis include peripheral sensory or autonomic neuropathy, cardiomyopathy, and GI dysfunction. As the disease progresses, symptoms can worsen and lead to life-threatening multiorgan dysfunction.

Hereditary transthyretin-mediated amyloidosis manifests as abnormal buildup of amyloids which are protein fibers that deposit in organs and tissues in consequence interfering with normal functioning. The amyloid deposits usually occur in the peripheral nervous system, which can result in a loss of sensation, pain, or immobility in the arms, legs, hands and feet. They can also deposit in the heart, kidneys, eyes and gastrointestinal tract and affect their functioning. The focus of the hATTR treatment is generally symptom management.

Given the magnitude of non-specific symptoms, diagnosis of hATTR is often challenging and is commonly confused with other conditions. Treatment options include liver transplantation and a limited number of pharmacologic therapies. While liver transplantation has been shown to eliminate the production of variant TTR protein and slow disease progression, it does not prevent cardiomyopathy as amyloids can continue to deposit in the heart. One treatment option is Vyndaqel (tafamidis), a transthyretin stabilizer, which stabilizes the tetramer of the TTR transport protein to slow the dissociation into monomers that drives TTR amyloidosis. Vyndaqel is indicated for the treatment of cardiomyopathy of wild type or hATTR amyloidosis. Recently approved treatment options for polyneuropathy of hATTR amyloidosis involve inhibition of hepatic

production of TTR using a gene silencing RNA molecule, Onpattro (patisiran), and an antisense oligonucleotide, Tegsedi (inotersen). Amvuttra (vutrisiran) is a double-stranded siRNA-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.

Clinical Studies:

NCT 04136184- NEURO-TTRansform- Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Study Population- Inclusion: aged 18 to 82 years at the time of informed consent; diagnosis of hereditary transthyretin-mediated polyneuropathy as defined by meeting all 3 of the following: Stage 1 or Stage 2 Familial Amyloid Polyneuropathy (FAP) or Coutinho Stage, documented genetic mutation in the TTR gene and symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including NIS ≥ 10 and ≤ 130. Exclusion: Karnofsky performance status ≤ 50; prior liver transplant or anticipated liver transplant within 1-yr of screening; New York Heart Association (NYHA) functional classification of ≥ 3; acute coronary syndrome within 6 months of screening or major surgery within 3 months of screening; current treatment with any approved drug for hereditary TTR amyloidosis.

Phase, Study Design, Sample Size- Randomized, open-label, multicenter clinical trial evaluating safety and efficacy of eplontersen in adult patients with polyneuropathy caused by hATTR amyloidosis N=168

Outcomes: Subjects were randomly assigned 6:1 to receive either eplontersen 45 mg subcutaneously once every 4 weeks (N=144) or inoterson 284 mg subcutaneously once weekly (N=24). Efficacy was based on the comparison of the eplontersen arm of study 1 (N=144) with an external placebo group (N=60) from the NEURO-TRR study. These studies had a comparable study population of adult patients with hereditary transthyretin-mediated amyloidosis associated polyneuropathy. The primary efficacy endpoints studied were the change from baseline to week 35 in the modified Neuropathy Impairment Scale +7 (mNIS+7) composite score and in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score and the adjusted mean percentage reduction in serum transthyretin concentrations. Eplontersen met the efficacy endpoints achieving a statistically significant and clinically meaningful change from baseline in mNIS+7 (difference, -9.0 [95% CI, -13.5, -4.5]; *P* <.001), Norfolk QoL-DN total score (difference, -11.8 [95% Ci, -16.8, -6.8] P<0.001), and percentage reduction in serum transthyretin concentration (difference, -66.4% [95% CI, -71.4%, -61.5%]; P<0.001) compared with the external placebo arm in the interim analysis at week 35. At 65 and 66 weeks, eplontersen demonstrated statistically significant and clinically meaningful change from baseline in serum transthyretin concentration (difference, -70.4% [95% CI, -75.2%, -65.7%]; P<0.001), mNIS+7 (difference, -24.8 [95% CI, -31.0, -18.6] P<0.001) and in Norfolk QoL-DN (difference, -19.7 [95% CI, -25.6, -13.8]; P<0.001). Eplontersen effect was also consistent across prespecified subgroups at week 66. Many of the patients that had an adverse reaction were mild in severity in the eplontersen group. Adverse reactions reported in at least >5% of patients treated with eplontersen include decreased vitamin A levels (15%), vomiting (9%), proteinuria (8%) injection site reactions (7%), blurred vision (6%) and cataract (5%). 6 eplontersen-treated patients discontinued the study due to a TEAE, but there were not any deaths related to the study drug.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Wainua (eplontersen) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Wainua (eplontersen): No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

Administer Wainua as soon as possible after a missed dose. Resume dosing at monthly intervals from the date of the most recently administered dose.

Wainua treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking Wainua. Higher doses than the recommended

daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with Wainua, as serum vitamin A levels do not reflect the total vitamin A in the body. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness, dry eyes).

CODING/BILLING 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

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Wainua SOAJ 45MG/0.8ML single-dose autoinjector

REFERENCES

1. Wainua (eplontersen) injection, for subcutaneous use [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2023.
2. Coelho, T., Marques, W., Jr, Dasgupta, N.R., Chao, C.-C., Parman, Y., França, M. C., Jr, Guo, Y.-C., Wixner, J., Ro, L-S., Calandra, C.R., Kowacs, P.A., Berk, J. L., Obici, L., Barroso. F. A., Weiler, M., Conceição, I., Jung, S. W., Buchele, G., Brambatti, M., & Chen, J. (2023). Eplontersen for Hereditary Trnsthyretin Amyloidosis With Polyneuropathy. *JAMA.* https://doi.org/10.1001/jama.2023.18688
3. Ando, Y., Coelho, T., Berk, J. L., Cruz, M. W., Ericzon, B. G., Ikeda, S., N Salvi, F. (2013). Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet journal of rare diseases*, *8*, 31. Doi:10.1186/1750-1172-8-31
4. Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. Ther Adv NeurolDisord. 2013 Mar; 6(2): 129–139
5. Alcantara, M., Mezei, M. M., Baker, S. K., Breiner, A., Dhawan, P., Fiander, A., … Bril, V. (2022). Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. Canadian Journal of Neurological Sciences, 49(1), 7–18. https://doi.org/10.1017/cjn.2021.34

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Prescriber Requirements References	Q3 2024
NEW CRITERIA CREATION	Q2 2024