09-J4000-77

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Reviewed: 06/11/25

Revised: 07/15/25

Subject: Eplontersen (Wainua)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Approximately 10,000 to 15,000 patients are diagnosed with hereditary transthyretin mediated (hATTR) amyloidosis in the United States. hATTR is a rare, progressive, and fatal multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver. Over time, these deposits cause significant neurologic problems, functional limitations, and disability. These presentations include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy [FAP]), and a predominantly cardiac phenotype (formerly known as familial cardiomyopathy), although the majority of cases express both neurologic and cardiac manifestations. hATTR profoundly impacts all aspects of quality of life. Given that the disease may affect multiple organ systems and may progress rapidly, a wide variety of manifestations may include (but are not limited to) weight loss, wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea. Some patients also develop cardiac complications, which can increase the risk of early death. The age of onset of symptoms, the types of problems patients experience, and the rate of progression vary significantly. Treatment options include liver transplant, diflunisal, patisiran (Onpattro™), and inotersen (Tegsedi™). In 2019, tafamidis meglumine (Vyndaqel®) and tafamidis (Vyndamax™) gained FDA approved for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM).

Eplontersen (Wainua), antisense oligonucleotide that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues, was approved by the U.S. Food and Drug Administration (FDA) in December 2023 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults.

The efficacy of eplontersen was evaluated in a randomized, open-label, phase 3 clinical trial of adult patients with hATTR-PN (NEURO-TTRansform, NCT04136184). All patients enrolled in the clinical trial were required to have mild to moderate polyneuropathy (Stage 1 or 2 FAP or Coutinho stage) and have

a genetic mutation in TTR gene. Participants were randomized to receive eplontersen 45 mg once every 4 weeks (n=144) or inotersen 284 mg once per week (n=24). Efficacy assessments were based on a comparison of the eplontersen arm of the NEURO-TTRansform trial with an external placebo group (n = 60) from the NEURO-TTR trial (NCT01737398) evaluating the change from baseline to week 35 in the modified Neuropathy Impairment Score +7 (mNIS+7) composite score and the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) total score.

In patients with hATTR-PN, those treated with eplontersen demonstrated a significantly greater reduction in adjusted mean serum transthyretin at week 65 (-81.7% vs -11.2%) and significantly lower (better) adjusted mean change from baseline to week 66 scores for the mNIS+7 composite score (0.3 vs 25.1) and for the Norfolk QoL-DN total score (-5.5 vs 14.2) compared with a historical group that received placebo (n=60) in the NEURO-TTR study.

Treatment-emergent adverse events (TEAEs) and serious TEAEs occurred in 97% and 15% of eplontersen-treated patients and 100% and 20% of placebo-treated patients, respectively. With eplontersen and historical placebo the following adverse events of special interest were reported: vitamin A deficiency/decreased or abnormal vitamin A (16% vs not reported), ocular events potentially related to vitamin A deficiency (17% vs 15%), thrombocytopenia (2% vs 2%), and glomerulonephritis (0% vs 3%).

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: Attruby, Vyndamax (ATTR-CM), Vyndaqel (ATTR-CM), and Wainua (ATTR-PN) are the preferred products for ATTR-CM and ATTR-PN

Initiation of eplontersen (Wainua) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with hereditary ATTR amyloidosis with polyneuropathy (hATTR-PN)
2. Member has a TTR mutation – laboratory documentation must be provided
3. Member is not a liver transplant recipient
4. Member demonstrates signs and symptoms of polyneuropathy – documentation from the medical record must be provided
5. Member's signs and symptoms of polyneuropathy are mild or moderate, defined as either of the following:
    a. Stage 1 or 2 FAP or Coutinho stage – documentation from the medical record must be provided
    b. Polyneuropathy disability score is less than or equal to IIIb – documentation from the medical record must be provided

6. Use will not be in combination with ANY of the following:
    a. Inotersen (Tegsedi)
    b. Patisiran (Onpattro)
    c. Tafamidis meglumine (Vyndaqel)
    d. Tafamidis (Vyndamax)
    e. Vutrisiran (Amvuttra)
7. Eplontersen is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 45 mg (1 syringe) every 4 weeks

Approval duration: 1 year

Continuation of eplontersen (Wainua) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of hATTR-PN (if another health plan, documentation of a health plan-paid claim for eplontersen during the 90 days immediately before the request must be submitted), **OR** the member has previously met all indication-specific criteria.
2. Member has a TTR mutation – laboratory documentation must be provided
3. Member is not a liver transplant recipient
4. Member demonstrates a clinically meaningful beneficial response to treatment with eplontersen compared to baseline – documentation from the medical record must be provided
5. Member's signs and symptoms of polyneuropathy are mild or moderate, defined as either of the following:
    a. Stage 1 or 2 FAP or Coutinho stage – documentation from the medical record must be provided
    b. Polyneuropathy disability score is less than or equal to IIIb – documentation from the medical record must be provided
6. Use will not be in combination with ANY of the following:
    a. Inotersen (Tegsedi)
    b. Patisiran (Onpattro)
    c. Tafamidis meglumine (Vyndaqel)
    d. Tafamidis (Vyndamax)
    e. Vutrisiran (Amvuttra)
7. Eplontersen is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 45 mg (1 syringe) every 4 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 45 mg administered by subcutaneous injection once monthly

Dose Adjustments

- None

Drug Availability

- 45 mg/0.8 mL in a single-dose autoinjector

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Reduced Serum Vitamin A Levels and Recommended Supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

BILLING/CODING INFORMATION:

HCPCS Coding

J3590	Unclassified biologic

ICD-10 Diagnosis Codes That Support Medical Necessity

E85.1	Neuropathic heredofamilial amyloidosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Familial Amyloid Polyneuropathy (FAP) stage: Clinical staging system for the neuropathy symptoms of hATTR (formerly termed familial amyloid neuropathy).

- The scale ranges from 1 to 3, as follows:
    - FAP Stage 1: Walking without assistance, mild neuropathy (sensory, autonomic, and motor) in lower limbs
    - FAP Stage 2: Walking with assistance, moderate impairment in lower limbs, trunk, and upper limbs
    - FAP Stage 3: wheelchair or bed-ridden, severe neuropathy

Modified neuropathy impairment score +7 (mNIS+7): A composite score measuring motor strength, reflexes, sensation, nerve conduction, and autonomic function. Two versions of this composite measure were adapted from the NIS+7 to better reflect hATTR polyneuropathy and have been used as primary outcomes in inotersen and patisiran clinical trials. Neither version of the mNIS+7 has a defined threshold for clinical relevance. A 2-point change has been suggested as the minimum clinically important difference for the NIS+7; 8 however, we were unable to find literature reporting any validation specific to either version of the mNIS+7. In both scales, a lower score represents better neurologic function (e.g., an increase in score reflects worsening of neurologic impairment).

Polyneuropathy disability score (PND): A five-stage measure of neuropathy impairment ranging from 0 (no impairment) to 4 (confined to a wheelchair or bedridden).

- Stage 0: no impairment
- Stage I: sensory disturbances but preserved walking capability
- Stage II: impaired walking capability but ability to walk without a stick or crutches
- Stage IIIA: walking only with the help of one stick or crutch
- Stage IIIB: walking with the help of two sticks or crutches
- Stage IV: confined to a wheelchair or bedridden

RELATED GUIDELINES:

Patisiran (Onpattro, 09-J3000-16)

Inotersen (Tegsedi), 09-J3000-17

OTHER:

None

REFERENCES:

1. AstraZeneca Pharmaceuticals. Wainua (eplontersen) injection. 2024. [cited 2/8/24]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7dcb847-71dd-4fff-82d0-d43a465fc096.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 2/8/24]. Available from: http://www.clinicalpharmacology.com/.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 2/8/24]. Available from: http://clinicaltrials.gov/.
4. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2/8/24].
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2/8/24]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

04/01/24	New Medical Coverage Guideline.
07/15/25	Revision to guideline; updated position statement