09-J4000-32

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Reviewed: 04/10/24

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Subject: Vutrisiran (Amvuttra)

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).

Vutrisiran (Amvuttra), a small interfering RNA (siRNA) that causes degradation of TTR mRNA through RNA interference resulting in a reduction of serum TTR protein and TTR protein deposits in tissues, was approved by the FDA in 2022 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

The safety and efficacy of vutrisiran were evaluated in a phase 3, randomized, open-label clinical trial (HELIOS-A, NCT03759379) of patients with hATTR polyneuropathy. Patients were randomized 3:1 to received vutrisiran 25 mg subQ every 3 months (n=122) or 0.3 mg/kg patisiran IV every 3 weeks (n=42) as a reference group. Of the vutrisiran-treated patients, 97% completed at least 9 months of treatment.

For efficacy assessments, an external placebo group (n=77) from another study of a similar population was used for comparison (APOLLO, NCT01960348).

The primary outcome, mean change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7), was significantly lower with vutrisiran compared with placebo at 9 months (-2.2 vs 14.8; mean difference, -17 points; 95% CI, -21.8 to -12.2). The mNIS+7 assesses neuropathy objectively on a scale from 0 to 304 points, with a lower number indicating less impairment/fewer symptoms. Secondary outcomes, such as quality of life (QOL), as assessed by the change from baseline in the Norfolk QOL-diabetes neuropathy (DN) score (-3.3 vs 12.9; mean difference, -16.2 points; 95% CI, -21.7 to -10.8), was significantly improved with vutrisiran compared with placebo at 9 months. The Norfolk QOL-DN assesses neuropathy subjectively on a scale from -4 to 136 points, with a lower number indicating less impairment/fewer symptoms. Additionally, the change from baseline in gait speed in 10-meter walk test and modified BMI (BMI x serum albumin) significantly favored vutrisiran compared with placebo with a treatment difference of 0.13 meters/second (95% CI, 0.07 to 0.19; a higher number indicates less disability/less impairment) and 67.8 mBMI (95% CI, 43 to 92.6).

POSITION STATEMENT:

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

1. Member is diagnosed with hereditary ATTR (hATTR) amyloidosis with polyneuropathy or familial amyloid polyneuropathy (FAP)
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. Member's 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. Eplontersen (Wainua)
    b. Inotersen (Tegsedi)
    c. Tafamidis meglumine (Vyndaqel)
    d. Tafamidis (Vyndamax)
    e. Patisiran (Onpattro)
7. Vutrisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 25 mcg every 3 months

Approval duration: 1 year

Continuation of vutrisiran (Amvuttra) **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 hereditary ATTR (hATTR) amyloidosis or familial amyloid polyneuropathy (FAP), **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 vutrisiran compared to baseline
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. Member's 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. Eplontersen (Wainua)
    b. Inotersen (Tegsedi)
    c. Tafamidis meglumine (Vyndaqel)
    d. Tafamidis (Vyndamax)
    e. Patisiran (Onpattro)
7. Vutrisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 25 mcg every 3 months

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

- 25 mg administered by subcutaneous injection once every 3 months
- Should administered by a healthcare professional

Dose Adjustments

- None

Drug Availability

- Injection: 25 mg/0.5 mL in a single-dose prefilled syringe

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

J0225	Injection, vutrisiran, 1 mg

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: BCBSF 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.

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 Sodium (Onpattro), 09-J3000-16

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

GUIDELINE UPDATE INFORMATION:

09/15/22	New Medical Coverage Guideline.
01/01/23	Revision: Added HCPCS code J0225 and deleted code J3490.
05/15/24	Review and revision to guideline; updated position statement and references.