09-J5000-50

Original Effective Date: 03/15/26

Reviewed: 02/11/26

Revised: 07/01/26

Subject: Transthyretin Amyloidosis (ATTR)

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, acoramidis (Attruby), eplontersen (Wainua), patisiran (Onpattro™), 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).

Acoramidis (Attruby)

Acoramidis (Attruby), a selective TTR stabilizer, was approved by the U.S. Food and Drug Administration (FDA) in November 2024 for use in the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular deaths and cardiovascular-related hospitalization.

The efficacy of acoramidis was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 611 adult patients with wild-type or variant (hereditary or de novo) ATTR-CM (NCT03860935).

Participants were randomized (2:1) to receive acoramidis 712 mg (n=409) or placebo (n=202) twice daily for 30 months. Treatment assignment was stratified by type of ATTR-CM [variant (ATTRv-CM) or wild-type (ATTRwt-CM)], NT-proBNP level, and estimated glomerular filtration rate (eGFR). The mean age of study participants was 77 years, 90.8% were male, 87.9% were White, 4.7% Black or African American,

2.1% Asian, 5.3% race other, 19% had a history of permanent pacemaker and 58% had a history of atrial fibrillation. No significant imbalance in baseline characteristics was observed between the two treatment groups.

Participants were permitted to initiate open-label tafamidis after 12 months in the study. A total of 107 participants received tafamidis: 61 (14.9%) in the ACORAMIDIS arm and 46 (22.8%) in the placebo arm. The median time to initiation of tafamidis for these 107 participants was 17 months.

The primary composite endpoint included all-cause mortality (ACM) and cumulative frequency of cardiovascular-related hospitalizations (CVH) over 30 months, analyzed hierarchically using the stratified Finkelstein-Schoenfeld (F-S) test. The F-S test demonstrated a statistically significant reduction (p=0.018) in ACM and cumulative frequency of CVH in the acoramidis arm versus the placebo arm. All-cause mortality was reported in 19% and 26% of participants in the acoramidis and placebo groups, respectively. The majority (79%) of the deaths were cardiovascular. Cardiovascular-related hospitalization was reported in 27% and 43% of participants in the acoramidis and placebo groups, respectively. The mean number of CVH events was 0.3 vs 0.6 per year. The majority (59%) of CVH were heart failure hospitalizations reported in 13% and 26% of the participants in the acoramidis and placebo groups, respectively.

The treatment effect of acoramidis on functional capacity and health status was assessed by the 6MWD and the Kansas City Cardiomyopathy Questionnaire-Overall Summary score (KCCQ-OS) respectively. At month 30, the LS mean difference (95% CI) in change from baseline in 6MWD was 40 [21, 58] meters ($p < 0.0001$) and change from baseline in KCCQ-OS was 10 [6, 14] points ($p < 0.0001$).

There was a higher frequency of gastrointestinal (GI) adverse reactions such as diarrhea 11.6% versus 7.6% and upper abdominal pain 5.5% versus 1.4% in the acoramidis versus placebo group, respectively. The majority of these GI adverse reactions were categorized as mild and resolved without drug discontinuation. A similar proportion of acoramidis-treated and placebo-treated participants discontinued study drug because of an adverse event (9.3% and 8.5%, respectively).

Eplontersen (Wainua)

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%).

Patisiran (Onpattro)

Patisiran (Onpattro), a double-stranded siRNA 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, was approved by the U.S. Food and Drug Administration (FDA) in August 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

The safety and efficacy of patisiran were evaluated in in a randomized, double-blind, placebo-controlled phase III trial (APOLLO) in adults with polyneuropathy caused by hATTR amyloidosis. Adult patients 18 to 85 years of age were eligible for the study if the investigatory estimated survival to be ≥ 2 years, Neuropathy Impairment Score (NIS) of 5 to 130, and polyneuropathy disability score ≤ IIIb. Patients were randomized in to receive intravenous patisiran at a dose of 0.3 mg/kg (n = 148) or placebo (n = 77) once every 3 weeks for 18 months. All patients were premedicated with a corticosteroid, acetaminophen, and antihistamines. The primary efficacy endpoint was the change at 18 months from baseline to month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7), an objective assessment of neuropathy that measures deficits in cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The maximum possible score was 304, with higher scores associated with greater disease severity. The clinical meaningfulness of changes in the mNIS+7 was assessed by a patient-reported assessment (the Quality of Life-Diabetic Neuropathy or QoL-DN total score) that evaluates the subjective experience of neuropathy the change from baseline in terms of physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy from baseline to month 18.

Patisiran demonstrated statistically and clinically significant differences from placebo for both scores (see table 1). Overall patisiran reduced the mean max serum TTR reduction by 87.8% from baseline in the patisiran treated group over 18 months. The LS mean change in the mNIS+7 from baseline at 18 months was -33.99 (p = 9.26x10-24); (Patisiran -6.03; placebo +27.96). The LS mean change in the Norfolk QOL-DN from baseline at 18 months was -21.1 (p = 1.10x10-10); (Patisiran -6.7; placebo +14.4). All secondary endpoints (e.g., NIS-W, R-ODS, COMPASS-31, etc.) also achieved statistical significance at 18 months.

The investigators also concluded that patisiran therapy was relatively safe and well tolerated with no increases in the frequency of events for patisiran compared to placebo group by system organ class.

Overall, 13 deaths occurred in the APOLLO study, however, none of these were considered related to the study drugs and were consistent with natural history. The majority of infusion-related reactions were mild in severity, with no severe or life-threatening, or serious reactions.

Table 1: Clinical Efficacy Results from the Placebo-Controlled Study

	Baseline, Mean (SD)		Change from Baseline to Month 18, LS Mean (SEM)		Patisiran-Placebo Treatment Difference, LS Mean (95% CI)	
Endpoint	Patisiran N=148	Placebo N=77	Patisiran	Placebo		p-value
Primary						
mNIS+7	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0 (-39.9, -28.1)	p<0.001
Secondary						
Norfolk QoL-DN	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	p<0.001
10-meter walk test (m/sec)	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	p<0.001

mBMI	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	p<0.001
CI, confidence interval; LS, least squares; mBMI, modified body mass index; mNIS, modified Neuropathy Impairment Score; QoL-DN, Quality of Life – Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean						

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel)

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel), selective TTR stabilizers, were approved by the U.S. Food and Drug Administration (FDA) in May 2019 for use in the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

The safety and efficacy of tafamidis were evaluation in a randomized, double-blind phase 3 trial (ATTR-ACT) of patients with transthyretin amyloid cardiomyopathy (n=441). Patients were randomized to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. The primary endpoint was all-cause mortality, followed by frequency of cardiovascular-related hospitalizations. Key secondary end points were the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), in which higher scores indicate better health status.

In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs. 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test (P<0.001) and a lower rate of decline in KCCQ-OS score (P<0.001). The incidence and types of adverse events were similar in the two groups.

Vutrisiran (Amvuttra)

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:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline 09-J5000-54, Drug Waste Reduction.

Site of Care: If patisiran (Onpattro) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46, Site of Care Policy for Select Non-Oncology Medications.

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

Acoramidis (Attruby)

Initiation of acoramidis (Attruby) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Diagnosis of cardiomyopathy due to hereditary transthyretin amyloidosis (hATTR) OR wild type transthyretin amyloidosis (ATTRwt) – documentation from the medical record must be provided
2. Past medical history of heart failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required/requires treatment with a diuretic for improvement) – documentation from the medical record must be provided
3. Left ventricular wall (interventricular septum or left ventricular posterior wall) thickness is equal to or greater than 12 mm – echocardiogram results must be provided
4. Presence of a variant TTR genotype and/or TTR precursor protein identification by immunohistochemistry, scintigraphy, or mass spectrometry – laboratory documentation must be provided
5. New York Heart Association (NYHA) classification of I, II, or III – documentation from the medical record must be provided
6. No evidence of primary (light chain) amyloidosis
7. None of the following clinical situations apply:
    a. Prior liver transplantation
    b. Prior heart transplantation
    c. Implanted cardiac mechanical assist device
8. Use will not be in combination with ANY of the following:

a. Vutrisiran (Amvuttra)
b. Eplontersen (Wainua)
c. Patisiran (Onpattro)
d. Tafamidis (Vyndamax, Vyndaqel)

9. Acoramidis is prescribed by (or in consultation with) a cardiologist, neurologist, geneticist, or physician specializing in the treatment of amyloidosis
10. Dose does not exceed 712 mg twice daily (4 tablets/day)

Approval duration: 1 year

Continuation of acoramidis (Attruby) meets the definition of **medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of cardiomyopathy due to either hereditary ATTR (hATTR) or wild type ATTR (ATTRwt) OR the member has previously met all indication-specific criteria
2. Member demonstrates a clinically meaningful beneficial response to treatment with acoramidis compared to baseline – documentation from the medical record must be provided
3. Use will not be in combination with ANY of the following:
    a. Vutrisiran (Amvuttra)
    b. Eplontersen (Wainua)
    c. Patisiran (Onpattro)
    d. Tafamidis (Vyndamax, Vyndaqel)
4. Acoramidis is prescribed by (or in consultation with) a cardiologist, neurologist, geneticist, or physician specializing in the treatment of amyloidosis
5. Dose does not exceed 712 mg twice daily (4 tablets/day)

Approval duration: 1 year

<u>Eplontersen (Wainua)</u>

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. Patisiran (Onpattro)
b. Tafamidis meglumine (Vyndaqel)
c. Tafamidis (Vyndamax)
d. 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. Patisiran (Onpattro)
    b. Tafamidis meglumine (Vyndaqel)
    c. Tafamidis (Vyndamax)
    d. 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

Patisiran (Onpattro)

Initiation of patisiran (Onpattro) **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 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. Acoramidis (Attruby)
    b. Eplontersen (Wainua)
    c. Inotersen (Tegsedi)
    d. Tafamidis meglumine (Vyndaqel)
    e. Tafamidis (Vyndamax)
    f. Vutrisiran (Amvuttra)
7. Member has tried and had an inadequate response to treatment with Wainua – documentation from the medical record must be provided
8. Patisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
9. Dose does not exceed the following:
    a. Weight less than 100 kg: 0.3 mg/kg (up to 30 mg) once every 3 weeks
    b. Weight greater than 100 kg: 30 mg once every 3 weeks

Approval duration: 1 year

Continuation of patisiran (Onpattro) **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 patisiran compared to baseline – documentation from the medical record must be provided
5. 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. Acoramidis (Attruby)
    b. Eplontersen (Wainua)
    c. Inotersen (Tegsedi)
    d. Tafamidis meglumine (Vyndaqel)
    e. Tafamidis (Vyndamax)
    f. Vutrisiran (Amvuttra)
7. Patisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis

8. Dose does not exceed the following:
    a. Weight less than 100 kg: 0.3 mg/kg (up to 30 mg) once every 3 weeks
    b. Weight greater than 100 kg: 30 mg once every 3 weeks

Approval duration: 1 year

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel)

Initiation of tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Diagnosis of cardiomyopathy due to hereditary transthyretin amyloidosis (hATTR) OR wild type transthyretin amyloidosis (ATTRwt) – documentation from the medical record must be provided
2. Presence of a variant TTR genotype and/or TTR precursor protein identification by immunohistochemistry, scintigraphy, or mass spectrometry – laboratory documentation must be provided
3. New York Heart Association (NYHA) classification of I, II,or III – documentation from the medical record must be provided
4. None of the following clinical situations apply:
    a. Prior liver transplantation
    b. Prior heart transplantation
    c. Implanted cardiac mechanical assist device
5. Use will not be in combination with ANY of the following:
    a. Acoramidis (Attruby)
    b. Eplontersen (Wainua)
    c. Patisiran (Onpattro)
    d. Vutrisiran (Amvuttra)
6. Tafamidis or tafamidis meglumine is prescribed by (or in consultation with) a cardiologist, neurologist, geneticist, or physician specializing in the treatment of amyloidosis
7. Dose does not exceed the following:
    a. Vyndaqel: 80 mg daily
    b. Vyndamax: 61 mg daily

Approval duration: 1 year

Continuation of tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of cardiomyopathy due to either hereditary ATTR (hATTR) or wild type ATTR (ATTRwt) OR the member has previously met all indication-specific criteria
2. Member demonstrates a clinically meaningful beneficial response to treatment with tafamidis compared to baseline – documentation from the medical record must be provided
3. Use will not be in combination with ANY of the following:
    a. Acoramidis (Attruby)

b. Eplontersen (Wainua)
c. Patisiran (Onpattro)
d. Vutrisiran (Amvuttra)

4. Tafamidis or tafamidis meglumine is prescribed by (or in consultation with) a cardiologist, neurologist, geneticist, or physician specializing in the treatment of amyloidosis
5. Dose does not exceed the following:
    a. Vyndaqel: 80 mg daily
    b. Vyndamax: 61 mg daily

Approval duration: 1 year

Vutrisiran (Amvuttra)

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

1. Member is diagnosed with either of the following and all associated criteria are met:
    a. Polyneuropathy (PN) due to hereditary transthyretin amyloidosis (hATTR) AND all of the following – documentation from the medical record must be provided
        i. Member demonstrates signs and symptoms of polyneuropathy – documentation from the medical record must be provided
        ii. Member's signs and symptoms of polyneuropathy are mild or moderate, defined as either of the following:
            1. Stage 1 or 2 familial amyloid polyneuropathy (FAP) or Coutinho stage – documentation from the medical record must be provided
            2. Member's polyneuropathy disability score is less than or equal to IIIb – documentation from the medical record must be provided
    b. Cardiomyopathy (CM) due to hereditary transthyretin amyloidosis (hATTR) OR wild type transthyretin amyloidosis (ATTRwt) AND all of the following – documentation from the medical record must be provided
        i. Past medical history of heart failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required/requires treatment with a diuretic for improvement) – documentation from the medical record must be provided
        ii. End-diastolic interventricular septal wall thickness is greater than 12 mm – echocardiogram results must be provided
        iii. New York Heart Association (NYHA) classification of I, II, or III – documentation from the medical record must be provided
        iv. No evidence of primary (light chain) amyloidosis
2. Member has a TTR mutation – laboratory documentation must be provided
3. Member is not a liver transplant recipient
4. 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)
f. Acoramidis (Attruby)

5. Member has tried and had an inadequate response to treatment with:
    a. ATTR-CM: Attruby AND Vyndaqel or Vyndamax – documentation from the medical record must be provided
    b. ATTR-PN: Wainua – documentation from the medical record must be provided
6. Vutrisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
7. Dose does not exceed 25 mg 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 amyloidosis with polyneuropathy or cardiomyopathy , **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. For ATTR-PN: 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)
    f. Acoramidis (Attruby)
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 mg every 3 months

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

FDA-approved

Acoramidis (Attruby)

- 712 mg orally twice daily (with or without food)

Eplontersen (Wainua)

- 45 mg administered by subcutaneous injection once monthly

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- Vyndamax: 61 mg (one 61-mg tafamidis capsule) orally once daily
- Vyndaqel: 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily
- VYNDAMAX and VYNDAQEL are not substitutable on a per mg basis

Dose Adjustments

Acoramidis (Attruby)

- None

Eplontersen (Wainua)

- None

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- None

Drug Availability

Acoramidis (Attruby)

- Tablets: 356 mg

Eplontersen (Wainua)

- Injection: 45 mg/0.8 mL of eplontersen as a clear, colorless-to-yellow solution in a single-dose autoinjector

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- Vyndamax: 61 mg tafamidis capsule
- Vyndaqel: 20 mg tafamidis meglumine capsule

PRECAUTIONS:

Boxed Warning

Acoramidis (Attruby)

- None

Eplontersen (Wainua)

- None

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- None

Contraindications

Acoramidis (Attruby)

- None

Eplontersen (Wainua)

- None

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- None

Precautions/Warnings

Acoramidis (Attruby)

- Increase in Serum Creatinine and Decrease in eGFR

Eplontersen (Wainua)

- Reduced Serum Vitamin A Levels and Recommended Supplementation

Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel))

- None

BILLING/CODING INFORMATION:

HCPCS Coding

J3590	Unclassified biologic (eplontersen)
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified (acoramidis, tafamidis, tafamidis meglumine)

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:

None

OTHER:

None

REFERENCES:

1. AstraZeneca Pharmaceuticals. Wainua (eplontersen) injection. 2026. [cited 2/1/26]. 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. BridgeBio. ATTRUBY (acoramidis) tablet, film coated. 2026 [cited 2/1/26]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=913552ef-875d-4cb7-bf05-a7d20a394c38
3. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2026 [cited 2/1/26]. Available from: http://www.clinicalpharmacology.com/.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 2/1/26]. Available from: http://clinicaltrials.gov/.
5. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2/1/26].
6. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med 2024; 390:132-142.
7. Maurer MS, Schwartz JH, Gundapaneni B, et al: Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018; 379(11):1007-1016.
8. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2026 [cited 2/1/26]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
9. Pfizer. Vyndamax, Vyndaqel (tafamidis) capsule. 2026 [cited 2/1/26]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1b4121ee-a733-4456-a917-be2603477839

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

03/15/26	New Medical Coverage Guideline: Merging MCGs 09-J3000-41, Tafamidis (Vyndamax, Vyndaqel) Oral, 09-J4000-77, Eplontersen (Wainua), 09-J3000-16 Patisiran (Onpattro™), 09-J4000-32 Vutrisiran (Amvuttra), and 09-J5000-11, Acoramidis (Attruby).
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.
07/01/26	Revision: Added Site of Care statement to the Position Statement.