Regence Oregon and Utah | Regence Idaho and select counties of Washington

Independent licensees of the Blue Cross and Blue Shield Association

Medication Policy Manual **Policy No:** dru733

Topic: Medications for Transthyretin-Mediated Amyloidosis

Date of Origin: January 15, 2023

- Amvuttra, vutrisiran
- Attruby, acoramidis
- Onpattro, patisiran
- Vyndamax, tafamidis
- Vyndaqel, tafamidis meglumine
- Wainua, eplontersen

Committee Approval Date: July 9, 2026 **Next Review Date:** 2027

Effective Date: September 1, 2026

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used for the treatment of transthyretin mediated amyloidosis (ATTR), which is a rare, progressive disease that can affect the nervous system, heart, and other major organs.

Policy/Criteria

Most contracts require pre-authorization approval of medications for ATTR amyloidosis prior to coverage.

I. Continuation of therapy (COT):

Medications for ATTR amyloidosis may be considered medically necessary for COT when both criterion A and B below are met.

A. One of the following (1, 2, or 3) is met:

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission

AND

B. **Amvuttra and Onpattro only**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for ATTR amyloidosis may be considered medically necessary when both criteria A and B below are met.

A. **Amvuttra and Onpattro only**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

AND

B. Clinical documentation (such as chart notes) that all the following criteria in the table below are met (Diagnosis, Coverable Medications, Diagnostic Criteria, and Step Therapy):

Diagnosis	Coverable Medications	Diagnostic Criteria	Step Therapy
ATTR-CM	• Amvuttra (vutrisiran) • Attruby (acoramidis) • Vyndamax (tafamidis) • Vyndaqel (tafamidis meglumine)	**1.** Diagnosis of wild-type or hereditary (variant) ATTR-CM was established by a specialist in cardiology. **AND** **2.** Diagnosis confirmed by genetic testing (TTR gene mutation), biopsy, immunohistochemical analysis, scintigraphy, or mass spectrometry. **AND** **3.** Symptomatic NYHA functional class I, II, or III, defined as at least one of the following (a or b): **a.** History of ≥ 1 heart failure-related hospitalization. **OR** **b.** Presence of heart failure symptoms requiring ongoing treatment with a diuretic. Heart failure symptoms include but are not limited to dyspnea, shortness of breath, volume overload, fluid retention, or peripheral edema.	For Amvuttra (vutrisiran) only: ≥ 18 months of Vyndamax/Vyndaqel (tafamidis) or ≥ 3 months of Attruby (acoramidis) was ineffective, or *both* were not tolerated or are contraindicated.
hATTR-PN	• Amvuttra (vutrisiran) • Onpattro (patisiran) • Wainua (eplontersen)	**1.** Diagnosis of hATTR-PN was established by a specialist in neurology, cardiology, amyloidosis, or genetics. **AND** **2.** Diagnosis confirmed by genetic testing (TTR gene mutation). **AND** **3.** Impairment due to neuropathy with a Polyneuropathy Disability (PND) score between I-IIIb or Familial Amyloid Polyneuropathy (FAP) Stage 1 or Stage 2 (as defined in *Appendix 1*). **AND** **4.** Symptoms consistent with polyneuropathy (see *Appendix 2*).	None
Both ATTR-CM and hATTR-PN (mixed phenotype)	• Amvuttra (vutrisiran) • Combination of stabilizer with silencer (see *Table 1*)	**1.** Diagnostic Criteria must be met for **both*** ATTR-CM and hATTR-PN, as detailed above. Note: This does **not** include ATTR-CM step therapy criteria. **AND** **2.** For Amvuttra (vutrisiran) only: Will be used as monotherapy (i.e., not in combination with another silencer or stabilizer). ***** If the patient is already established on treatment for ATTR-CM and has a new diagnosis of hATTR-PN, only current criteria for hATTR-PN plus mixed phenotype step therapy must be met (and vice versa).	For combination of stabilizer with silencer only: ≥ 6 months of Amvuttra (vutrisiran) was ineffective, not tolerated, or is contraindicated.

Key: ATTR-CM=cardiomyopathy of transthyretin-mediated amyloidosis; hATTR-PN= polyneuropathy of hereditary transthyretin-mediated amyloidosis; NYHA=New York Heart Association; TTR= transthyretin

III. Administration, Quantity Limitations, and Authorization Period:

A. Regence Pharmacy Services considers Amvuttra (vutrisiran), Onpattro (patisiran), and Wainua (eplontersen) prefilled syringe coverable only under the medical benefit (as provider-administered medications).

B. Regence Pharmacy Services considers Attruby (acoramidis), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), and Wainua (eplontersen) autoinjector coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, medications for ATTR amyloidosis will be authorized in the following quantities and for the following authorization periods outlined in *Table 1* below.

Table 1: Medications for ATTR amyloidosis

Authorization Limits
Cardiomyopathy of transthyretin-mediated amyloidosis (ATTR-CM) **STABILIZERS** - Vyndamax (tafamidis): Up to 30 of the 61 mg tablets per 30 days. - Vyndaqel (tafamidis meglumine): Up to 120 of the 20 mg tablets per 30 days. - Attruby (acoramidis): Up to 112 of the 356mg tablets per 28 days. **SILENCERS** - Amvuttra (vutrisiran): Up to 4 injections of a 25 mg prefilled syringe in a one-year period. Authorization **shall** be reviewed at least every twelve months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability, improvement in heart failure symptoms, reduction in hospitalizations, or improvement of NYHA functional class.
Polyneuropathy of hATTR amyloidosis (hATTR-PN) **SILENCERS** - Amvuttra (vutrisiran): Up to 4 injections of a 25 mg prefilled syringe in a one-year period. - Onpattro (patisiran): Patients < 100kg: Up to 18 infusions in a one-year period based on dose of 0.3 mg/kg every 3 weeks. Patients ≥ 100kg: Up to 18 infusions in a one-year period based on a dose of 30 mg every 3 weeks. - Wainua (eplontersen): Up to one autoinjector or prefilled syringe per 28 days. Note: The prefilled syringe requires administration by a health care professional. Authorization **shall** be reviewed at least every twelve months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met as and that the medication is providing clinical benefit, including stability or improvement in symptoms consistent with polyneuropathy.

IV. Investigational Uses: Medications for ATTR amyloidosis are considered investigational when used for all other conditions, including but not limited to:

A. Combination use of more than one stabilizer (see *Table 1*) for any indication (cardiomyopathy, polyneuropathy, mixed phenotype).

B. Combination use of more than one silencer (see *Table 1*) for any indication (cardiomyopathy, polyneuropathy, mixed phenotype).

C. Other forms of amyloidosis not specified above.

V. Not-Medically Necessary Uses

A. Combination use of any silencer with any stabilizer for the same indication (see *Table 1*).

Position Statement

Summary

- Medications for transthyretin-mediated (ATTR) amyloidosis may be covered for specific diagnoses where there is demonstrated safety and efficacy from randomized, controlled trials to support their use, including treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM), polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN), and mixed phenotype ATTR (both cardiac and neurological manifestations).
  - Amvuttra (vutrisiran) and Onpattro (patisiran) are small interfering RNA (siRNA) medications that silence the transthyretin (TTR) gene resulting in a reduction of serum and tissue TTR concentrations.
  - Wainua (eplontersen) is an RNA oligonucleotide that works by silencing the TTR gene resulting in a reduction of serum and tissue TTR concentrations.
  - Amvuttra (vutrisiran), Onpattro (patisiran), and Wainua (eplontersen) are known as silencers. Amvuttra (vutrisiran) is the only silencer with indications for both ATTR-CM and hATTR-PN, whereas Onpattro (patisiran) and Wainua (eplontersen) are indicated only for the treatment of hATTR-PN.
  - Attruby (acoramidis), Vyndamax (tafamidis), and Vyndaqel (tafamidis meglumine) are transthyretin (TTR) stabilizers that selectively bind to specific sites of the TTR tetramer to prevent destabilization and amyloid fibril formation. These stabilizers have indications only for the treatment of ATTR-CM.
- The intent of the policy is to allow coverage of medications for patients with ATTR-CM and/or hATTR-PN when the diagnosis is established by a specialist and diagnostic tests, there is symptomatic impairment, and step therapy has been met when appropriate, as detailed in the coverage criteria. The policy criteria are based on the specific clinical requirements of the pivotal trials, to target these therapies among patients for whom the clinical benefit has been demonstrated.
- In the pivotal trials, the mortality benefit versus placebo was observed at 18 months, 3 months, and 6 months for Amvuttra (vutrisiran), Attruby (acoramidis), Vyndamax (tafamidis), and Vyndaqel (tafamidis meglumine).

- Amvuttra (vutrisiran) provides the best value for patients with a mixed phenotype diagnosis as it is the only monotherapy option.
- In the absence of direct comparison trials among any available treatment options for ATTR *(see Table 1*), it is unknown whether any single treatment option is more efficacious than another for any manifestation of ATTR, or whether combination therapy is more efficacious than monotherapy.
- Despite being studied in a population that was treated with tafamidis (40% at baseline), the evidence from the Amvuttra (vutrisiran) pivotal trial was insufficient to establish whether combination therapy with Amvuttra (vutrisiran) and tafamidis was superior to either therapy alone.
- Medications for ATTR amyloidosis may be covered at the doses proven to be safe and effective in the clinical trials (as outlined in *Table 1* of the coverage criteria above). The safety and effectiveness of higher doses has not been established. Use of medications for ATTR amyloidosis in clinical settings other than described in the coverage criteria is considered investigational.
- The safety and efficacy of combining more than one silencer, or more than one stabilizer, for any indication has not been established and is considered investigational.
- The combination use of any stabilizer with any silencer for the same indication is considered not medically necessary, as there are no published trials demonstrating superiority of combination use compared to monotherapy.

<u>hATTR-PN</u>

- hATTR-PN medications are known as silencers and include Onpattro (patisiran), Amvuttra (vutrisiran), and Wainua (eplontersen), as listed in *Table 1*.
- The effectiveness of hATTR-PN medications was demonstrated in phase 3 randomized, controlled trials, in patients with genetically confirmed hATTR amyloidosis and symptomatic polyneuropathy (familial amyloidosis polyneuropathy [FAP] Stage 1 or 2).
- All hATTR-PN medications slowed the progression of neurologic worsening and decline in quality of life, as well as improved neurologic function and quality of life compared to placebo.
- Genetic testing is required to confirm the diagnosis of hATTR amyloidosis.
- There is insufficient evidence that any one medication for the treatment of hATTR-PN is superior to another as there are currently no comparative trials.

<u>ATTR-CM</u>

- The effectiveness of ATTR-CM medications was demonstrated in phase 3, randomized, placebo-controlled trials, in adults with symptomatic ATTR-CM (wild-type or hereditary) and NYHA FC I-III. Attruby (acoramidis), Amvuttra (vutrisiran), Vyndamax (tafamidis), and Vyndaqel (tafamidis meglumine) each improved all-cause mortality and reduced cardiovascular-related hospitalizations at 30 months as compared to placebo.
- The specific clinical criteria in the pivotal trials required patients to demonstrate a significant level of symptomatic heart failure burden. At present, there is not adequate evidence to evaluate the effectiveness of these medications for very early-stage disease.
- There is insufficient evidence that any one medication for the treatment of ATTR-CM is superior to another as there are currently no comparative trials.

- A genetic test that detects variants in the TTR gene is the gold standard for confirming a diagnosis of hATTR-CM. To date, there are more than 150 known pathogenic mutations in the TTR gene; the clinical presentation (cardiac, neuropathic, mixed phenotype, and other organ involvement) can vary depending on the specific mutation.
- Some methods used to diagnose wild-type ATTR-CM include tissue biopsies, immunohistochemical analysis, scintigraphy, or mass spectrometry.
- Of note, Vyndamax (tafamidis) 61 mg and Vyndaqel (tafamidis meglumine) 80 mg and Vyndamax (tafamidis) 61 mg are bioequivalent.

Clinical Efficacy

hATTR-PN

Background [1-6]

- hATTR amyloidosis is a rare, rapidly progressing condition, caused by an autosomal-dominant inherited mutation in the TTR gene resulting in misfolded protein accumulating as amyloid fibrils in nerves, heart, gastrointestinal tract, or other tissues, leading to progressive disability and loss of function in major organs presenting as neurological, cardiac, or mixed phenotype.
- Neurologic phenotype, also known as familial amyloid polyneuropathy (FAP), manifests as sensorimotor polyneuropathy with a high variability in symptoms impacting quality of life such as pain, numbness, muscle weakness, weight loss/wasting, focal nerve lesions, and autonomic dysfunction, while patients with a cardiac phenotype experience cardiomyopathy leading to heart failure.
- Symptom onset can occur anywhere between the ages of 20-70 years, is often misdiagnosed without family history of disease, and can only be confirmed with biopsy and genetic confirmation of the TTR mutation.
- Life expectancy once diagnosed is between 5-12 years, though often shorter in patients with cardiomyopathy, with death attributed to cardiac dysfunction, infection, and cachexia.
- There are no consensus U.S. treatment guidelines. However, the 2022 Canadian Neurological Sciences Foundation guidelines recommend Onpattro (patisiran) as a first line agent. Guidelines have not been updated since the approval of the newer TTR silencers (Amvuttra and Wainua).
- Liver transplant was the previous standard of care in early disease but does not prevent progression as the wild type TTR may continue to circulate and expand amyloid deposits and is no longer recommended as first line treatment.
- Vyndamax/Vyndaqel (tafamidis) and diflunisal stabilize TTR protein and are sometimes used in this indication off-label. Tafamidis failed to receive FDA approval or this indication due to not meeting statistical significance. Diflunisal does not reverse course of disease and has limitations due to long term risks of adverse effects.
- Endpoints in trials included modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN). [7 8]
    * The mNIS+7 is an exam-based assessment of neuropathy which includes measures of nerve fiber conduction, sensory testing, and autonomic measures (postural blood pressure). Higher scores indicate worse neurologic function.

* The Norfolk QOL-DN evaluates patients' perception of impairment with respect to physical functioning/large fiber neuropathy, activities of daily living, neuropathy symptoms, small fiber neuropathy, and autonomic dysfunction. Higher scores indicate poorer quality of life.

Onpattro (patisiran) [1 9-11]

- Efficacy of Onpattro (patisiran) was demonstrated in the APOLLO study, an 18-month, phase 3 randomized, placebo-controlled trial. Patients were required to meet the following requirements for enrollment:
  * FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
  * Diagnosis of hATTR confirmed by genetic testing and biopsy.
  * Symptoms of neuropathy measured by NIS, a tool used to measure motor, sensory, and reflex function.
  * Patients with a history of liver transplantation were excluded.
- The primary endpoint was change in mNIS+7 from baseline. Change in Norfolk QOL-DN score was a secondary endpoint.
- Results showed that Onpattro (patisiran) improved neurologic symptoms and improved quality of life compared to placebo. There is limited data on its effect on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.
- A recent phase 3b open-label, single arm trial (N=23) demonstrated efficacy of Onpattro (patisiran) in patients post liver transplant.
  * Patients had received a liver transplant 12 months prior to study, and had experienced polyneuropathy progression post-transplant, defined as an increase of PND.
  * PND scores of IV were excluded from the trial, as well as past use of Onpattro (patisiran) or Tegsedi (inotersen).
- The primary endpoint of serum TTR reduction showed statistically significant reduction with the median percent reduction from baseline at 12 months of 91%. Secondary endpoints of mean improvements from baseline of NIS of -3.7 and Norfolk QOL-DN of -6.5, support the primary endpoints and are in line with the results from the primary APOLLO trial for which Onpattro (patisiran) previously was approved.

Amvuttra (vutrisiran) [3 12 13]

- Efficacy of Amvuttra (vutrisiran) was demonstrated the HELIOS-A study, an 18-month, phase 3 randomized, externally placebo-controlled trial.
  * Patients were required to meet the following requirements for enrollment:
    - A diagnosis of hATTR confirmed by the presence of a TTR gene mutation.
    - Polyneuropathy disability (PND) score between I-IIIb, which equates to being FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
    - Symptoms of neuropathy measured using NIS scoring between 5-130.
    - Patients with a history of liver transplantation were excluded.
    - Patients treated with TTR stabilizers (tafamidis or diflunisal) must have been off therapy for 14 days prior to enrollment to be included.

    * Patients were randomized 3:1 to be treated with Amvuttra (vutrisiran) 25 mg every 3 months or a reference comparator Onpattro (patisiran) 0.3 mg/kg every 3 weeks, respectively for 18 months.
    * Efficacy data was determined by comparing the Amvuttra (vutrisiran) population (n=122) of the HELIOS-A trial to the external placebo group (n=77) from the APOLLO trial above (for which Onpattro [patisiran] received FDA approval when compared to the same placebo group).
    * The inclusion/exclusion criteria and endpoints from the external placebo group in the APOLLO trial were the same in the HELIOS-A trial.
    * Baseline characteristics were similar between groups, however in the APOLLO trial, patients appeared to have more severe disease compared to the HELIOS-A trial with a baseline mNIS+7 of 74.6 vs 60.6, and Norfolk QOL-DN total score 55.5 vs 47.1, respectively.
    * The primary endpoint was the mean change in mNIS+7 from baseline at 9 months. Mean change in Norfolk QOL-DN score and the 10-meter walk test (10-MWT) were secondary endpoints at 9 and 18 months (mNIS+7 was also a secondary endpoint at 18 months).
    * Results showed that Amvuttra (vutrisiran) improved neurologic symptoms (mNIS+7 change from baseline was -2.2 in Amvuttra [vutrisiran] arm vs 14.76 in placebo at 9 months; -0.46 vs 28.09 at 18 months), quality of life (change from baseline in Norfolk QOL-DN was a -3.3 vs 12.9 compared to placebo at 9 months; -1.2 vs 19.8 at 18 months), and gait speed (change from baseline in 10-MWT was -.133 vs 0 compared to placebo at 9 months; -.264 vs -.02 at 18 months).
- Use of an external placebo vs active comparator and the external placebo having more severe baseline disease are of a concern, however patients in the Amvuttra (vutrisiran) arm showed large statistical significance across all endpoints at 9 and 18 months compared to placebo, results were seen across all subgroups, and the disease did not follow the normal course of progression.
- Amvuttra (vutrisiran) also showed non-inferiority when looking at exploratory endpoints comparing the serum concentrations of TTR protein to the active comparator group of Onpattro (patisiran) patients at 18 months.

Wainua (eplontersen) [14-16]

- Efficacy of Wainua (eplontersen) was demonstrated the NEURO TTRansform study, a 66-week, phase 3 randomized, externally placebo-controlled trial.
    * Patients were required to meet the following requirements for enrollment:
        - A diagnosis of hATTR confirmed by the presence of a TTR gene mutation.
        - PND score between I-IIIb, which equates to being FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
        - Symptoms of neuropathy measured using the NIS scoring between 10-130. The NIS is a tool used to measure motor, sensory, and reflex function.
        - Patients with a history of liver transplantation were excluded.
        - Patients treated with TTR stabilizers (tafamidis or diflunisal) must have been off therapy for 14 days prior to enrollment to be included.

    * Patients were randomized 6:1 to be treated with Wainua (eplontersen) 45 mg every month or a reference comparator Tegsedi (inotersen) 300 mg weekly, respectively for 35 weeks, with all patients transferred over to Wainua (eplontersen) from week 36 on.
    * Efficacy data was determined by comparing the Wainua (eplontersen) population (n=140) of the NEURO TTRansform trial to the external placebo group (n=59) from the NEUROTTR trial above, (for which Tegsedi [inotersen] received FDA approval when compared to the same placebo group).
    * The inclusion/exclusion criteria and endpoints from the external placebo group in the NEUROTTR trial were the same in the NEURO TTRansform trial.
    * Baseline characteristics were similar between groups, however in the NEURO TTR trial, patients appeared to have less severe disease compared to the NEURO TTRansform trial with a baseline mNIS+7 of 74.8 vs 81.3, respectively.
    * The primary efficacy endpoints were the mean change in mNIS+7 from baseline at 35 and 66 weeks. Mean change in Norfolk QOL-DN score was the pivotal secondary endpoint at 35 and 66 weeks.
    * Results showed that Wainua (eplontersen) improved neurologic symptoms (mNIS+7 change from baseline was 0.2 in Wainua (eplontersen) arm vs 9.2 in placebo at 35 weeks; 0.3 vs 25.1 at 66 weeks), quality of life (change from baseline in Norfolk QOL-DN was -3.1 vs 8.7 compared to placebo at 35 weeks: -5.5 vs 14.2 at 66 weeks).
    * Use of an external placebo vs active comparator confounds interpretation of the results; however, patients in the Wainua (eplontersen) arm showed large statistical significance across all endpoints at 35 and 66 weeks compared to placebo, results were seen across all subgroups, and the disease did not follow the normal course of progression.
- There is currently no data on the effect of Wainua (eplontersen) on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.

ATTR-CM

Background [17-20]

- ATTR-CM is a rare, late-onset, life-threatening disease associated with restrictive cardiomyopathy and progressive heart failure. It is caused by the deposition of misfolded TTR protein in the heart tissues that leads to the formation of amyloid fibrils. Formation of amyloid fibrils leads to organ damage and dysfunction.
- Misfolding and aggregation of TTR in ATTR-CM occurs in the context of genetically normal (wild-type) protein (wild type ATTR-CM) or in the context of substitution or deletion mutations in the TTR gene (hereditary or variant ATTR-CM).
- ATTR-CM, regardless of type, typically manifests as heart failure, characterized by dyspnea, edema, syncope, volume overload, sudden cardiac death, pericardial disease, thromboembolism, stroke. Extracardiac manifestations can include the development of autonomic or peripheral nerve disease.
- Several methods, including tissue biopsies, nuclear scintigraphy, and cardiac MRI, are used to determine the presence of amyloidosis. A genetic test that detects variants in the TTR gene distinguishes between hereditary and wild-type amyloidosis.

- The prevalence is estimated to be 45 in 100,000. The number of newly diagnosed cases is expected to increase in the next five years due to increased disease awareness and diagnosis. The age of onset for hereditary (variant) ATTR-CM is typically between 30 and 50, while wild-type typically occurs between ages 60 and 70.
- Median survival without treatment is reported to be 2.5 to 3.5 years after diagnosis. However, the evidence for the natural history of ATTR-CM is limited to small trials.
- Guideline-recommended treatment is divided into management of heart failure symptoms (e.g., edema, dyspnea, volume overload, risk of thromboembolism, arrythmias) and the use of disease-modifying treatments such as tafamidis. Attruby (acoramidis) has not been formally included into treatment guidelines (its approval was after the most recent guideline update), but it is mentioned as a promising upcoming agent. Amvuttra (vutrisiran), as the newest FDA-approved agent for ATTR-CM, has not yet been included in the most recent guidelines.
- A liver transplant is only (rarely) indicated in hereditary ATTR-CM and was the previous standard of care. Liver transplant is not an option for wild type ATTR-CM, as it only potentially reduces the formation of new TTR protein but has no impact on the existing, circulating misfolded TTR protein or existing TTR amyloid fibrils. Combined liver/heart transplants could be performed in select patients with both wild type and hereditary ATTR-CM; however, this approach is rarely used in practice as these patients are often of advanced age with poor long-term survival.

Vyndamax (tafamidis) and Vyndaqel (tafamidis meglumine) [17 18]

- The efficacy of Vyndaqel (tafamidis meglumine) was established in a single 30-month phase 3, placebo-controlled, randomized-controlled trial (ATTR-ACT).
    * In the primary analysis, Vyndaqel (tafamidis meglumine) demonstrated an improvement in survival rates and reduction in CV-related hospitalizations in patients with ATTR-CM as compared to placebo.
    * Subjects were included in the study if they had a diagnosis of wild-type or hereditary ATTR-CM and a history of heart failure-related hospitalizations or heart failure symptoms which required additional treatment (e.g., diuretics).
    * Subjects with NYHA functional class IV, a history of liver and/or heart transplant, or those who had an implanted cardiac device were excluded from the trial. It is unclear if these patients will receive clinical benefit from Vyndaqel (tafamidis meglumine).
- In a bioequivalence study, Vyndamax (tafamidis) 61 mg and Vyndaqel (tafamidis meglumine) 80 mg demonstrated no clinically significant pharmacokinetic differences.
- Trials of Vyndaqel (tafamidis meglumine) excluded patients with prior liver and/or heart transplant. There are no published clinical trials evaluating the safety or efficacy of tafamidis-containing medications for the treatment of ATTR-CM in patient with prior liver and/or heart transplant.

Attruby (acoramidis) [21-25]

- The efficacy of Attruby (acoramidis) was established in a single, 30-month, phase 3, placebo-controlled trial (ATTRibute-CM). Subjects received acoramidis or placebo twice daily.

    * Subjects were included in the study if they had a diagnosis of wild-type or hereditary ATTR-CM and a history of heart failure-related hospitalizations or heart failure symptoms which required ongoing diuretics.
    * Subjects with NYHA functional class IV, or those who had an implanted cardiac device were excluded from the trial.
    * Attruby (acoramidis) demonstrated an improvement in survival rates and reduction in CV-related hospitalizations in patients with ATTR-CM as compared to placebo. A reduction in NT-proBNP levels (a biomarker whose increase is correlated with worsening symptoms) and an improvement in the 6-minute walking distance (a measure of functionality) were also demonstrated.
    * Of note, the use of open label tafamidis was allowed in the trial after 12 months. About 18% of subjects, between both treatment groups, used concomitant tafamidis. An FDA-review concluded that the evidence on concomitant therapy with tafamidis is inconclusive (small number of patients, small number of events in patients on concomitant therapy, and limited follow-up time post tafamidis initiation). The review noted that at 12 months, acoramidis stabilization of transthyretin would have been maximized and sufficient to impart its clinical efficacy and that the addition of tafamidis would not have substantially contributed to the results of the trial.
- There are no head-to-head trials comparing tafamidis to acoramidis; in the absence of such trials, there is currently no true clinical distinction between these two agents regarding efficacy or safety.

Amvuttra (vutrisiran)[26-28]

- The efficacy of Amvuttra (vutrisiran) was established in a single, 30-month, phase 3, placebo-controlled trial (HELIOS-B). Subjects received vutrisiran or placebo subcutaneously once every 3 months.
    * Subjects were included in the trial if they had a diagnosis of ATTR-CM (wild type or hereditary) and a history of heart failure-related hospitalizations or heart failure symptoms which required ongoing diuretics.
    * Subjects with NYHA Functional Class IV and those with any other type of non-TTR mediated cardiomyopathy or other type of amyloidosis were excluded from the trial.
    * At baseline, 40% of subjects in the overall population were on tafamidis. Other concomitant medications allowed in the trial were SGLT2 inhibitors and loop diuretics (30% and 80% of the overall population, respectively). The use of concomitant medications was open-label and not randomized.
    * Two populations were assessed at 36 months: the overall population (those with or without baseline tafamidis) and the monotherapy population (those without baseline tafamidis):
        ▪ Amvuttra (vutrisiran) demonstrated a reduction in the primary composite endpoint of all-cause mortality (ACM) and recurrent cardiovascular (CV) events, including CV hospitalizations and urgent heart failure (HF) visits in both the overall and monotherapy populations [hazard ratio (HR) 0.72 p=0.01, and HR 0.67 p=0.02, respectively].

    - Clinically relevant reductions in mortality and CV events were noted, but the HRs between both populations were similar.
    - The trial lacked sufficient power to detect differences in risk reduction between combination (vutrisiran and tafamidis) and monotherapy (vutrisiran alone).
    - The trial allowed for the use of non-randomized concomitant medications with CV benefits (tafamidis, SGLT2i); given that these agents have varying CV efficacy, their use in an open-label, non-randomized manner could potentially confound the observed efficacy results for vutrisiran.
- There is insufficient evidence to evaluate the effectiveness of these therapies for early-stage disease. The pivotal trials enrolled patients with a significant level of symptomatic heart failure burden, for whom the clinical benefit has been demonstrated.
- There is insufficient evidence to conclude that combination therapy with Amvuttra (vutrisiran) and Vyndamax/Vyndaqel (tafamidis) is superior to Amvuttra (vutrisiran) treatment alone.
- In the absence of comparative efficacy between agents, it remains unclear whether any single ATTR-CM treatment is superior to others, and whether combining a silencer (reduces TTR production) with a TTR stabilizer (prevents misfolding) offers greater benefits than monotherapy.

Appendices

Appendix 1: Staging of hATTR amyloidosis with polyneuropathy [4 5]

FAP Stage	Symptoms	Modified Polyneuropathy Disability (PND) Score
0	Asymptomatic	N/A
I	Mild, ambulatory, symptoms at lower limbs limited	I. Sensory disturbances in extremities but preserved walking capacity II. Difficulties in walking but without the need for a walking stick
II	Moderate, further neuropathic deterioration, ambulatory but requires assistance	IIIa. One stick or one crutch required for walking IIIb. Two sticks or two crutches required for walking
III	Severe, bedridden/wheelchair bound with generalized weakness	IV. Patient confined to a wheelchair or bed

Appendix 2: Symptoms of Polyneuropathy [3]

Peripheral sensorimotor polyneuropathy Symptoms	Autonomic neuropathy symptoms
Tingling or increased pain in the hands, feet, hands and/or arms,	Orthostasis
Loss of feeling in the hands and/or feet, numbness or tingling in the wrists,	Abnormal sweating
Loss of ability to sense temperature,	Sexual dysfunction
Difficulty with fine motor skills	Recurrent urinary tract infections
Seizures	Dysautonomia (constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety)

Cross References
Treatment of Hereditary Transthyretin-Mediated Amyloidosis in Adult Patients, BlueCross BlueShield Association (BCBSA) Medical Policy, MPRM 5.01.30; [March 2026]
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J0222	Injection, patisiran (Onpattro), 0.1 mg.
HCPCS	J0225	Injection, vutrisiran (Amvuttra), 1 mg

References

1. Onpattro [prescribing information]. San Diego, CA: Alnylam Pharmaceuticals, Inc.
2. Amvuttra [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
3. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Clinical Review for NDA 215515; vutrisiran (Amvuttra™). Secondary Center for Drug Evaluation and Research; U.S. Food and Drug Administration Clinical Review for NDA 215515; vutrisiran (Amvuttra™) [cited 8/24/2022]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215515Orig1s000MedR.pdf.
4. Adams D, Ando Y, Beirao JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. J Neurol. Germany, 2021:2109-22.
5. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol.* 2016;29 Suppl 1:S14-26. PMID: 26734952
6. Alcantara M, Mezei MM, Baker SK, et al. Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. Can J Neurol Sci. England, 2022:7-18.
7. Institute for Clinical and Economic Review (ICER). Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Final Report. Oct 4, 2018.
8. National Institute for Health and Care Excellence (NICE) Guidance. Inotersern for treating hereditary transthyretin amyloidosis. May 22, 2019.
9. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med.* 2018;379(1):11-21. PMID: 29972753
10. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. England, 2017:181.
11. Schmidt HH, Wixner J, Plante-Bordeneuve V, et al. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. *Am J Transplant.* 2022;22(6):1646-57. PMID: 35213769
12. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2022:1-9. PMID: 35875890
13. Yarlas A, Lovley A, Brown D, et al. Responder analysis for neuropathic impairment and quality-of-life assessment in patients with hereditary transthyretin amyloidosis with polyneuropathy in the NEURO-TTR study. J Neurol. Germany, 2022:323-35.
14. Coelho T, Marques W, Jr., Dasgupta NR, et al. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. JAMA. United States, 2023:1448-58.
15. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Integrated Review for NDA 217388; eplontersen (Wainua™). Secondary Center for Drug Evaluation and Research; U.S. Food and Drug Administration Integrated Review for NDA 217388; eplontersen (Wainua™) [cited 2/9/2024]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217388Orig1s000IntegratedR.pdf.
16. Wainua [prescribing information]: AztraZeneca Pharmaceuticals.
17. Vyndaqel, Vyndamax (tafamidis) [Prescribing Information]. New York, NY: Pfizer.
18. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med.* 2018;379(11):1007-16. PMID: 30145929
19. Fontana MM. Cardiac Amyloidosis: Epidemiology, clinical manifestations, and diagnosis;www-uptodate-com, 2024.
20. Writing C, Kittleson MM, Ruberg FL, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2023;81(11):1076-126. PMID: 36697326
21. Attruby [Prescribing Information], BridgeBio Pharma.
22. New Drug Review (Attruby) IPD Analytics; www.ipdanalytics.com 2024.
23. Center for Drug Evaluation and Research; US Food and Drug Administration Clinical Review for NDA 216540, Attruby (acoramidis). 11/20/2024 ed, 2024.

24. Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM); NCT03860935. 06/27/2024 ed, 2024.
25. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. *N Engl J Med.* 2024;390(2):132-42. PMID: 38197816
26. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. *N Engl J Med.* 2025;392(1):33-44. PMID: 39213194
27. HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149. 2/17/2025 ed, 2025.
28. Amvuttra for the treatment of ATTR-CM; IPD Analytics; www.ipdanalytics.com 2025.

Revision History

Revision Date	Revision Summary
7/9/2026	Added new Wainua (eplontersen) pre-filled syringe to Authorization Limits table.
4/2/2026	No criteria changes with this annual review.
7/10/2025	• Added coverage criteria for Amvuttra (vutrisiran) for ATTR-CM indication. • Added new criteria for mixed phenotype population, with a step through Amvuttra for combination use of a silencer and stabilizer.
4/3/2025	Effective 7/1/25: • Added Attruby (acoramidis) to policy for ATTR-CM, same coverage criteria as Vyndamax/Vyndaqel (tafamidis/tafamidis meglumine). • Clarified certain criteria for ATTR-CM: - Diagnosis established BY (not in consultation with) a specialist in cardiology. - Genetic test added as a diagnostic method. - Added "Symptomatic" NYHA FC I-III, defined per trial criteria. • Removed requirement for "no prior liver transplant" for ATTR-PN agents and requirement for "no prior liver/heart transplants" for ATTR-CM agents given no clinical advantage to select for one agent over another in these populations. • Removed Tegsedi (inotersen) from the policy (removed from market 9/2024).
12/12/2024	No criteria changes with this annual review.
6/20/2024	• Added newly FDA-approved drug Wainua (eplontersen) for polyneuropathy of hATTR amyloidosis in patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptomatic impairment due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria (effective 9/1/2024). • Added Amvuttra and Onpattro to site of care (SOC) program (effective 10/1/2024).
3/21/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	New combination policy (effective 1/15/2023): • Combined the following medication policies: dru577 Onpattro, patisiran, dru579 Tegsedi, inotersen, and dru595 tafamidis-containing medication; no change to intent of pre-existing criteria.

Revision Date	Revision Summary
	• Added newly FDA-approved drug Amvuttra (vutrisiran), for polyneuropathy of hATTR amyloidosis in patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptomatic impairment due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria • Removed requirement for "no prior liver transplant" for Onpattro (patisiran). • For polyneuropathy criteria: - Clarified intent of "functional impairment" criterion to "symptomatic impairment" based on trial data and staging of polyneuropathy. - Removed Onpattro (patisiran) from "no previous liver transplant" criterion.

Drug names identified in this policy are the trademarks of their respective owners.