RNA-Targeted Therapies (Amvuttra™ and Onpattro®)

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Instructions for Use

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Coverage Rationale

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Amvuttra (vutrisiran) and Onpattro (patisiran) are proven for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis.

Amvuttra (vutrisiran) is medically necessary for the treatment of the polyneuropathy of hATTR amyloidosis in patients who meet all of the following criteria:

- For initial therapy, all of the following:
  - Both of the following:
    - Diagnosis of hATTR amyloidosis with polyneuropathy
    - Documentation that the patient has a pathogenic TTR mutation (e.g., V30M)

    and
  - Documentation of one of the following:
    - Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
    - Patient has a baseline familial amyloid polyneuropathy (FAP) Stage 1 or 2
    - Patient has a baseline neuropathy impairment score (NIS) ≥ 5 and ≤ 130
    - Patient has a baseline Karnofsky performance status (KPS) score ≥ 60%

    and
  - Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); and
  - Patient has not had a liver transplant; and
  - Patient is not receiving Amvuttra in combination with any of the following:
    - RNA interference agents [e.g., Onpattro (patisiran), Tegsedi (inotersen)]
    - Transthyretin stabilizers [e.g., Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis)]

    and
  - Prescribed by or in consultation with a neurologist; and
  - Dosing is in accordance with the US Food and Drug Administration prescribing information; and
  - Initial authorization is for no more than 12 months.

- For continuation of therapy, all of the following:
  - Patient has previously received treatment with Amvuttra
    and
  - Documentation of one of the following:
    - Patient continues to have a PND score ≤ IIIb
    - Patient continues to have a FAP stage 1 or 2
    - Patient continues to have a NIS score ≥ 5 and ≤ 130
    - Patient continues to have a KPS score ≥ 60%

    and
  - Documentation that the patient has experienced a positive clinical response to Amvuttra (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); and
  - Patient is not receiving Amvuttra in combination with any of the following:
    - RNA interference agents [e.g., Onpattro (patisiran), Tegsedi (inotersen)]
    - Transthyretin stabilizers [e.g., Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis)]

    and
  - Prescribed by or in consultation with a neurologist; and
  - Dosing is in accordance with the US Food and Drug Administration prescribing information; and
  - Authorization is for no more than 12 months.

Onpattro (patisiran) are medically necessary for the treatment of the polyneuropathy of hATTR amyloidosis in patients who meet all of the following criteria:

- For initial therapy, all of the following:
  - Both of the following:
    - Diagnosis of hATTR amyloidosis with polyneuropathy
    - Documentation that the patient has a pathogenic TTR mutation (e.g., V30M)

    and
  - Documentation of one of the following:
    - Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
    - Patient has a baseline familial amyloid polyneuropathy (FAP) Stage 1 or 2
    - Patient has a baseline neuropathy impairment score (NIS) ≥ 5 and ≤ 130

    and
  - Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); and
  - Patient has not had a liver transplant; and
  - Patient is not receiving Onpattro in combination with any of the following:
    - RNA interference agents [e.g., Amvuttra (vutrisiran), Tegsedi (inotersen)]]
    - Transthyretin stabilizers [e.g., Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis)]

    and
  - Prescribed by or in consultation with a neurologist; and
  - Dosing is in accordance with the US Food and Drug Administration prescribing information; and
  - Initial authorization is for no more than 12 months.
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with Onpattro; and
  - Documentation of one of the following:
    - Patient continues to have a PND score ≤ IIIb
    - Patient continues to have a FAP Stage 1 or 2
    - Patient continues to have a NIS score ≥ 5 and ≤ 130

    and
  - Documentation that the patient has experienced a positive clinical response to requested drug (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); and
  - Patient is not receiving Onpattro in combination with any of the following:
    - RNA interference agents [e.g., Amvuttra (vutrisiran), Tegsedi (inotersen)]
    - Transthyretin stabilizers [e.g., Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis)]

    and
  - Prescribed by or in consultation with a neurologist; and

- Dosing is in accordance with the US Food and Drug Administration prescribing information; and
- Authorization is for no more than 12 months.

Onpattro (patisiran) is unproven and not medically necessary for the treatment of:
- Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis
- Primary or leptomeningeal amyloidosis

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0222	Injection, patisiran, 0.1 mg
J0225	Injection, vutrisiran, 1 mg

Diagnosis Code	Description
E85.1	Neuropathic heredofamilial amyloidosis

Background

Hereditary ATTR (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy, is a progressive, disabling and life-threatening polyneuropathy affecting the peripheral and autonomic nervous system. This disease is an autosomal transmission disorder which is usually due to a point mutation of the transthyretin (TTR) gene. The disease is caused by misfolded transthyretin (TTR) protein that accumulates as amyloid fibrils in multiple organs, including the nerves, heart, and gastrointestinal tract.

Amvuttra (vutrisiran) and Onpattro (patisiran) are double-stranded small interfering RNAs (siRNAs) that target a sequence of mRNA conserved across wild-type and all TTR variants and can thereby degrade and reduce serum levels and protein deposits in tissues of both wild-type and mutated protein. It is formulated as lipid nanoparticles which direct it to the liver, the primary source of circulating TTR. Patisiran therapy is associated with observed lowering of TTR levels in both wild-type and mutant (V30M) forms of TTR.

A genetic testing service is available in the United States and Canada and a genetic counseling service is available in the United States. Medical professionals and patients may access information on the Alnylam Pharmaceuticals website.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

A randomized, double-blind, placebo-controlled, phase III, global study (APOLLO) evaluated the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy. 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 2:1 (n = 148:77) to receive either intravenous (IV) patisiran 0.3 mg/kg or placebo every 3 weeks. The primary endpoint was to determine the efficacy of patisiran at 18 months based on the difference in the change in modified NIS + 7 (a composite measure of motor strength, sensation, reflexes, nerve conduction, and autonomic function) between the patisiran and placebo groups. Secondary endpoints evaluated the effect of patisiran on Norfolk-Diabetic Neuropathy quality of life questionnaire score, nutritional status (as evaluated by modified body mass index), motor function (as measured by NIS-weakness and timed 10-m walk test), and autonomic symptoms (as measured by the Composite Autonomic Symptom Score-31 questionnaire). Exploratory objectives include assessment of cardiac function and pathologic evaluation to assess nerve fiber innervation and amyloid burden. Safety of patisiran was also assessed throughout the study. 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. These reactions decreased over time and led to treatment discontinuation in only 1 patient. The investigators concluded that patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo while significantly reducing disease symptoms and disability, improvement in quality of life, nutritional status, strength, and ambulation seen with patisiran relative to placebo.[1,8]

In a subpopulation analysis of the APOLLO trial, investigators evaluated the treatment association of patisiran with regional left ventricular (LV) myocardial strain in cardiac manifestation in hATTR.[11,12] The prespecified cardiac subpopulation (126 of 225 [56%]) comprised of patients with a baseline LV wall thickness of 13 mm or more and no history of hypertension or aortic valve disease. Of the 126 patients included in the prespecified cardiac subpopulation, 36 patients (28.6%) received placebo and 90 patients (71.4%) received patisiran. At baseline, LV global longitudinal strain (GLS) was impaired and regional longitudinal strains were lowest in the basal segments with apical sparing. There were no differences in regional longitudinal strains between the treatment groups at baseline. Patisiran improved the absolute GLS (least-squares mean [SE] difference, 1.4% [0.6%]; 95% CI, 0.3%-2.5%; p = .02) compared with placebo at 18 months, with the greatest differential increase observed in the basal region (overall least-squares mean [SE] difference, 2.1% [0.8%]; 95% CI, 0.6%-3.6%; p = .006) and no significant differences in the mid and apical regions among groups. Patisiran reduced mean left ventricular wall thickness (least-squares mean difference ±SEM: −0.9 ±0.4 mm, p = 0.017), interventricular septal wall thickness, posterior wall thickness, and relative wall thickness at month 18 compared with placebo. Patisiran also led to increased end-diastolic volume (8.3 ±3.9 mL, p = 0.036), decreased global longitudinal strain (−1.4 ±0.6%, p = 0.015), and increased cardiac output (0.38 ±0.19 L/min, p = 0.044) compared with placebo at month 18. Patisiran lowered N-terminal prohormone of brain natriuretic peptide at 9 and 18 months (at 18 months, ratio of fold-change patisiran/placebo 0.45,p < 0.001). A consistent effect on N-terminal prohormone of brain natriuretic peptide at 18 months was observed in the overall APOLLO patient population (n = 225). Median follow-up duration was 18.7 months. The exposure-adjusted rates of cardiac hospitalizations and all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively (Andersen–Gill hazard ratio, 0.54; 95% CI, 0.28–1.01). The authors concluded that patisiran prevented the deterioration of LV GLS and decreased mean LV wall thickness over 18 months, suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis.

The safety and efficacy of vutrisiran was established in a phase 3 randomized, open-label study (NCT03759379) in adult patients with polyneuropathy caused by hATTR amyloidosis. Patients eligible for the study met the following criteria: aged 18-25 years, diagnosis of ATTRv amyloidosis with a documented TTR variant and baseline NIS 5-130, polyneuropathy disability (PND) score ≤ IIIb, a KPS ≥ 60, and adequate liver and renal function. Patients were randomized 3:1 to receive 25 mg of vutrisiran subcutaneously once every 3 months (n = 122), or 0.3mg/kg patisiran intravenously every 3 weeks (n = 42) as a reference group. Efficacy assessments were based on a comparison of the vutrisiran with an external placebo group in another study (NCT01960348) composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis. The primary endpoint was the change from baseline to month 9 in modified Neuropathy Impairment Score + 7 (mNIS + 7). The mNIS + 7 has a total score range from 0 to 304 points, with higher scores representing a greater severity of disease. The least

squares mean change from baseline for the mNIS + 7 score was -2.2 for vutrisiran vs. + 14.8 for placebo (difference of -17.0, 95% CI: -21.8, -12.2; p < 0.001). The clinical meaningfulness of effects on the mNIS + 7 was assessed by the change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The Norfolk QoL-DN has a total score range from -4 to 136, with higher scores representing greater impairment. Additional endpoints were gait speed, as measured by the 10-meter walk test (10MWT), and modified body mass index (mBMI). The mean least squares mean change from baseline for the Norfolk QoL-DN total score was -3.3 for vutrisiran vs. + 12.9 for placebo (difference of -16.2, 95% CI: -21.7, -10.8; p < 0.001. The mean least squares mean change from baseline for the 10-meter walk test was 0 for vutrisiran vs. -0.13 for placebo (difference of 0.13, 95% CI; 0.07, 0.19; p < 0.001) and 10-meter walk test at Month 9 compared to placebo in the external study (p < 0.001). The mean least squares mean change from baseline for mBMI was 7.6 for vutrisiran vs. -60.2 for placebo (difference of 67.8, 95% CI; 43.0, 92.6; p < 0.001).

The most common adverse reactions (at least 5%) were arthralgia (11%), dyspnea (7%), and decreased vitamin A (7%). Patients were instructed to take the recommended daily allowance of vitamin A. Seventy-four percent of patients treated with vutrisiran had normal vitamin A levels at baseline, and 98% of those with a normal baseline developed low vitamin A levels. In some cases, the decreased vitamin A level was reported as an adverse reaction. Two serious adverse reactions of atrioventricular (AV) heart block (1.6%) occurred in patients treated with vutrisiran, including one case of complete AV block. Injection site reactions were reported in 5 (4%) patients treated with vutrisiran. Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild and transient.

Institute for Clinical and Economic Review (ICER)

On October 4th, 2018, ICER released a clinical report entitled, “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value”. ICER recommendations are as follows:[13]

- ICER judges the clinical evidence for patisiran to be “incremental” or “better”.
- On average, patients on patisiran demonstrated improvement in neuropathy symptoms, as measured by the mNIS + 7. Based on the current body of evidence, there is moderate certainty of a substantial net health benefit with high certainty of at least a small net health benefit compared to best supportive care.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Amvuttra™ (vutrisiran) is a transthyretin-directed small interfering RNA indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Onpattro® (patisiran) contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

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Policy History/Revision Information

Date	Summary of Changes
03/01/2023	Coverage Rationale *Amvuttra (Vutrisiran)* • Revised coverage criteria for: Initial Therapy ○ Replaced criterion requiring "the patient has a baseline neuropathy impairment score (NIS) ≥ *10* and ≤ 130" with "the patient has a baseline neuropathy impairment score (NIS) ≥ *5* and ≤ 130" Continuation of Therapy ○ Replaced criterion requiring "the patient continues to have a NIS score ≥ *10* and ≤ 130" with "the patient continues to have a NIS score ≥ *5* and ≤ 130" Supporting Information • Updated *Clinical Evidence* section to reflect the most current information • Archived previous policy version 2023D0072J

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.