Policy Number	**RX501.102**
Policy Effective Date	**02/01/2025**
Policy End Date	**12/31/2025**

Patisiran (Onpattro)

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Related Policies (if applicable)
RX501.146: Vutrisiran

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. See RX501.146 Vutrisiran (Amvuttra) and Patisiran (Onpattro) for dates of service 01/01/2026 and after.

Initial Therapy

Patisiran (Onpattro®) **may be considered medically necessary** for adult patients when used according to the U.S. Food and Drug Administration (FDA) approved label and **ALL** of the following are met:

1. Individual has a confirmatory diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) by a genetic test; AND
2. Presence of clinical signs and symptoms of polyneuropathy characterized by **ONE** of the following:
   - Baseline polyneuropathy disability (PND) IIIb or lower (see Table 1 in Description section); or
   - Baseline familial amyloid polyneuropathy (FAP) Stage one or two (see Table 1 in the Description section); AND
3. Individual does not have **ANY** of the following:
   - New York Heart Association (NYHA) class III or IV heart failure; or
   - Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.); or
   - Prior liver transplantation; AND
4. Individual will not use Onpattro® (patisiran) in combination with other transthyretin (TTR) reducing agents (e.g., tafamidis meglumine, vutrisiran, eplontersen, etc.).

Continuation Therapy

Continued use of patisiran (Onpattro®) **may be considered medically necessary** with documentation of:

1. Disease stability or improvement in symptoms (e.g., decrease in neuropathic pain, improved motor function, quality of life assessment, and/or serum TTR levels); **AND**
2. Individual is not receiving Onpattro® (patisiran) in combination with other TTR reducing agents (e.g., tafamidis meglumine, vutrisiran, eplontersen, etc.).

Patisiran (Onpattro®) **is considered experimental, investigational and/or unproven** in all other situations.

NOTE 1: Authorization approval duration (initial and reauthorization): 12 months.

Policy Guidelines

None.

Description

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant genetic disease with variable penetrance. Transthyretin is a transporter protein that carries thyroxine and retinol (vitamin A) and is primarily synthesized in the liver (95%) but also choroid plexus. The gene for transthyretin is located on chromosome 18. Variance in the transthyretin gene results in the production of misfolded transthyretin protein. More than 120 variants have been described, including single variants, compound heterozygotes, and deletions. The valine-to-methionine substitution at position 30 (V30M) is the most common variant observed worldwide, while valine-to-isoleucine substitution at position 122 (V122I) is the most common variant in the U.S. The misfolded protein generated because of a variant in the transthyretin gene is insoluble and accumulates as amyloid fibrils (i.e., amyloidosis) in multiple organs of the body, such as the liver, nerves, heart, and kidneys causing disruption of organ tissue structure and function.

Historically, hATTR was classified into 2 distinct syndromes—amyloidosis with polyneuropathy (previously known as familial amyloid polyneuropathy or FAP) and amyloidosis with cardiomyopathy (previously known as familial amyloid cardiomyopathy). (1) While hATTR patients may show predominance of polyneuropathy or cardiomyopathy, it is now recognized that most patients' manifest signs and symptoms of both syndromes over the course of their disease and, therefore, the current clinical approach treats FAP and familial amyloid cardiomyopathy as 1 hereditary disease with a spectrum of clinical manifestations. (2) The first symptoms of hATTR amyloidosis typically appear between the mid-20s and the mid-60s, involving multiple tissues and organs and often seem unrelated. Neurologic symptoms include severe sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and autonomic dysfunction resulting in orthostatic hypotension, diarrhea, impotence, and bladder disturbances. (3) While the neurologic symptoms of hATTR are among the most physically disabling, cardiac manifestations are the most predictive of early death. Cardiac manifestations include arrhythmias, conduction disorders, cardiomegaly, and heart failure. If the disease is untreated, the median survival for patients with predominantly neuropathic symptoms is 5 to 15 years, while patients with predominantly cardiomyopathic symptoms have a median survival of 2.5 to 6 years. (4, 5)

The FAP stage system and the polyneuropathy disability score are the 2 most used clinical staging systems and are summarized in Table 1. Higher scores on each of the staging systems are indicative of greater disease severity.

Table 1. Clinical Staging in Hereditary Transthyretin-Mediated Amyloidosis

FAP Stage	Clinical Description

Stage 0	No symptoms
Stage 1	Unimpaired ambulation
Stage 2	Assistance with ambulation required
Stage 3	Wheelchair-bound or bedridden
PND Score	
Stage 0	No symptoms
Stage I	Sensory disturbances but preserved walking capability
Stage II	Impaired walking capacity but ability to walk without a stick or crutches
Stage IIIA	Walking 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

Adapted from Ando et al. (2013) (3)
FAP: familial amyloid polyneuropathy; PND: polyneuropathy disability.

Diagnosis
Diagnosis of hATTR based on clinical signs and symptoms is difficult because of heterogeneity in clinical manifestations and the nonspecific nature of signs and symptoms that may mimic other conditions. Furthermore, the age of onset and rate of progression are highly variable from patient to patient. (2) As a result, many patients are misdiagnosed or their diagnosis is delayed, and patients often see physicians across multiple specialties before receiving an accurate diagnosis. (2)

To confirm the diagnosis, proven amyloid deposition in biopsy specimens and identification of a pathogenic variant in the transthyretin gene are necessary. (6) Amyloid deposition in the biopsied tissues can be confirmed by using Congo red staining and, ideally, immunohistochemical study as well as laser capture tandem mass spectrometry. However, mass spectrometry can only demonstrate a mass difference between wild-type and transthyretin protein variants in serum. It does not specify the site and kind of amino acid substitution in a number of disease-related transthyretin variants; thus, DNA sequencing is usually required. Sequence analysis of the transthyretin gene, the only gene in which mutation is known to cause hATTR, detects more than 99% of pathogenic variants. (6)

There are currently 2 genetic test programs that offer no-cost, confidential genetic testing and genetic counseling services sponsored by the manufacturers of inotersen and patisiran. These are summarized in Table 2.

Table 2. Characteristics of Genetic Testing Program Offered by Manufacturers in the U.S.

Program	Program Eligibility	Tests Offered	Detail
AlnylamAct™	Patients 18 years and older with a suspected diagnosis or a confirmed family	Invitae Cardiomyopathy Comprehensive Panel	Testing for ~50 genes associated with inherited cardiomyopathy

	history of hATTR amyloidosis.		conditions, including hATTR amyloidosis.
		Invitae Comprehensive Neuropathies Panel	Testing for ~70 genes that cause dominant, recessive, and X-linked hereditary neuropathies, including hATTR amyloidosis.
		Invitae Transthyretin Amyloidosis Test	Single-gene genetic testing for the TTR gene, which is associated with hATTR amyloidosis.
The hATTR Compass™ Program	Patients who are 18 years and older and who have a family history of or are experiencing symptoms of hATTR amyloidosis.	hATTR Amyloidosis Test	Single-gene test for TTR.
		CardioNext	Up to 85-gene panel targeting patients with cardiomyopathies, including hATTR amyloidosis.
		NeuropathySelect	80-gene panel targeting patients with hereditary neuropathies, including hATTR amyloidosis (available at select centers).

Adapted from AlnylamAct™ and The hATTR Compass™ Program (7, 8)
hATTR: hereditary transthyretin-mediated amyloidosis; TTR: transthyretin.

Epidemiology

It is estimated that the neuropathy-predominant form of hATTR affects at least 10,000 people worldwide, (9) and roughly 3,000-3,500 people in the United States (U.S.). (10) Due to under-diagnosis and a lack of population-based data, these numbers may underestimate the actual prevalence. (11) According to unpublished data from Alnylam, there may be 10,000 to 15,000 individuals with the neuropathy-predominant form of hATTR [AMCP dossier].

The prevalence of the cardiomyopathy form of hATTR is also problematic to estimate. About 50,000 people worldwide may have hATTR amyloidosis. (9, 10) In the U.S. general population, the prevalence of V122I variant (which is the most common variant seen in the U.S.) is 3.4%. (12) However, phenotypic penetrance resulting in overt clinical cardiac disease depends on age

and varies widely from 7% to 80%. (13) Higher estimates of clinical prevalence were reported in studies with very small samples of carriers. Characteristics of hATTR in the U.S. by different variants are summarized in Table 3.

Table 3. Characteristics of hATTR in the U.S. by Variants

Variant	Median Age at Symptoms Onset (Year)	Median Age at Diagnosis (Year)	Median Age at Death (Year)
T60A	60.2	64.5	67.6
V30M	64.3	67.8	74.7
V122I	63.7	69.3	72.9
S77Y	55.8	60.1	65.8
Other	53.1	56.7	62.1

Adapted from Swiecicki et al. (2015) (14)

Treatment

Prior to the approval of patisiran and inotersen in 2018, there was no U.S. Food and Drug Administration (FDA) approved treatment available in the U.S. for the treatment of hATTR. Management approaches included the use of pharmacotherapy with tetramer stabilizers (such as diflunisal and tafamidis) and surgery (orthotopic liver transplant).

Diflunisal, a generic nonsteroidal anti-inflammatory drug, is not approved by the FDA for the treatment of hATTR but is available in the U.S. as a generic and has been used off-label for treatment. Diflunisal has been shown to stabilize transthyretin tetramers in a phase I study, (15) and significantly reduced the progression of neurologic impairment and preserved the quality of life in a randomized controlled trial. (16) Although the results of the randomized controlled trial were positive, multiple limitations with long-term use of diflunisal such as gastrointestinal bleeding, worsening of renal insufficiency, and cardiovascular events (e.g., MI, stroke) preclude its long-term use. Furthermore, diflunisal does not reverse neurologic or cardiac impairment.

Tafamidis received FDA approval in 2019 for treatment of hATTR patients with cardiomyopathy.

As transthyretin is primarily formed in the liver, orthotopic liver transplantation has been the disease-modifying treatment available to most patients with hATTR. This procedure can remove approximately 95% of the production of variant transthyretin. However, limited organ availability, exclusion of older patients and those with advanced disease, the high costs of transplantation, the risks of lifelong immunosuppression, and reports of disease progression following liver transplantation limits it use. Furthermore, orthotopic liver transplantation is not recommended for patients with cardiac involvement due to the observed post-transplant progression of cardiac; making a considerable proportion of patients in the U.S. who will develop cardiomyopathy ineligible for transplantation. (17) As such the procedure is not commonly performed in the U.S.

Mechanism of Action

The function of small interfering ribonucleic acid (RNA) is to regulate gene expression, or how much protein will be made from a particular gene. Patisiran and vutrisiran are small interfering RNA that are designed to selectively target variant and wild-type transthyretin messenger RNA through RNA interference, which results in a reduction of serum transthyretin and transthyretin deposits in tissues. Inotersen and eplontersen are an antisense oligonucleotide that causes degradation of variant and wild-type transthyretin messenger RNA through binding to the transthyretin messenger RNA, which results in a reduction of serum transthyretin and transthyretin deposits in tissues.

Regulatory Status

In August 2018, patisiran (Onpattro, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Patisiran is given as an intravenous infusion based on body weight:

- For individuals weighing less than 100 kg: 0.3 mg/kg once every three weeks.
- For individuals weighing 100 kg or more: 30 mg once every three weeks.

Patisiran treatment requires premedication with intravenous corticosteroid, oral acetaminophen, intravenous H1 blocker, and intravenous H2 blocker prior to its administration to reduce the risk of infusion-related reactions. For premedications not available or not tolerated intravenously, equivalents may be administered orally.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and the ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events

and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis

Clinical Context and Therapy Purpose

The purpose of patisiran for individuals with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) is to provide a treatment option that is an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with hATTR.

Interventions

The therapy being considered is patisiran.

Comparators

Management approaches include the use of pharmacotherapy with tetramer stabilizers (such as diflunisal and tafamidis) and surgery (orthotopic liver transplant). Tafamidis is approved in the European Union and several South American and Asian countries, but not in the U.S. for the treatment of polyneuropathy. Orthoptic liver transplantation has also shown to be beneficial but is less frequently used in the U.S.

Outcomes

The general outcomes of interest are related to assessing the impact of disease on sensorimotor, autonomic and cardiovascular manifestations; summarized in Table 4.

Table 4. Description of Health Outcome Measures Relevant to Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis

Outcome	Objective	Description	MCID
mNIS+7	• Estimates progression of polyneuropathy and its impact on physical function. • Designed to assess both small and large fiber impairment in hATTR amyloidosis clinical trials.	• Two versions have been used in the 2 pivotal trials of patisiran and inotersen. • Multi-dimensional composite clinical measure of motor, sensory, and autonomic polyneuropathy. • Total score of 304 to 346.6 points with	• MCID for either version of mNIS+7 has not been defined. • A difference in 2 points for the original NIS score (the predecessor to the NIS+7 and the mNIS+7) is considered

		higher scores indicating worsening disease and disability. (18)	clinically meaningful. (19)
Norfolk-QOL	• Three domains measure small fiber, large fiber, and autonomic nerve function). (18) • Other 2 domains relate to symptoms and impacts on activities of daily living.	• Patient-reported 35-item composite quality-of-life measure. • Higher scores indicate a worsening of QOL. • It has been validated and demonstrated to be a reliable indicator of disease severity in hATTR amyloidosis with polyneuropathy. (20)	The MCID has not yet been reported in the literature. However, this measure has been demonstrated to distinguish between FAP stages. (20)
R-ODS Disability	Captures activity and social participation limitations in patients.	Patient-reported 24-item score where each item is scored as either 0 (unable to perform), 1 (able to perform but with difficulty), or 2 (able to perform without difficulty).	MCID has not yet been reported in the literature.
10-MWT	Performance measure that assesses walking speed in meters per second and can be used to measure functional mobility.	Higher values indicate faster gait speed.	Among older adults, including those with mobility disabilities and subacute stroke survivors, a mean increase of 0.05 m/s represents a small meaningful change in gait speed and of 0.10 m/s represents a substantial clinically meaningful change, based on distribution and anchor-based approaches. (21)

Grip Strength	Indicator of neuropathic progression and disability.	In hATTR amyloidosis, grip strength is used as an indicator of neuropathic progression and disability, and an inverse association between grip strength and the PND has been demonstrated.	A change in grip strength of 4.7 to 6.2 kg has been reported to be clinically meaningful. (22)
mBMI	Indicator of nutritional status in hATTR amyloidosis.	Higher values indicate better nutritional status.	MCID has not been established in hATTR amyloidosis.
COMPASS-31	It is a measure of autonomic neuropathy.	• It consists of 31 clinical questions with a total score ranging from 0 to 100 with higher scores indicating more symptoms and more frequent symptoms. • There are 6 autonomic domains: orthostatic intolerance (40 points), secreto-motor (15 points), gastrointestinal (25 points), bladder (10 points), vasomotor (5 points) and pupillomotor (5 points). (23)	MCID has not yet been reported in the literature.
PND score	Measures functional disability due to polyneuropathy.	See Table 1 for description.	Because functional impairment worsens with each higher level of PND score, any change of PND score can be considered clinically important.

EQ-5D	Measures quality of life.	• Dimension scores range from 1 to 5, with lower scores indicating worsening of QOL. • Utility scores range from 0 (death) to 1.0 (perfect health). (24) • A 100-point visual analogue scale is used to rate general patient health status.	MCIDs in utility values obtained with the EQ-5D may vary by disease and by anchor, (25) and MCIDs below 0.10 have been estimated. (26)

10-MWT: 10-meter walk test; COMPASS-31: Composite Autonomic Symptom Score-31; EQ-5D: Euro-QOL; FAP: familial amyloid polyneuropathy; hATTR: hereditary transthyretin-mediated; mBMI: modified body mass index; MCID: minimal clinically important difference; mNIS; modified neuropathy impairment score; NIS: neuropathy impairment score; PND: polyneuropathy disability; QOL: quality of life; R-ODS: Rasch-built-Overall Disability Scale.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

In one pivotal RCT of patisiran (APOLLO, NCT01960348) in 225 adults with hATTR amyloidosis with polyneuropathy, participants were randomized to receive either patisiran or placebo (Table 5). (27) There were several differences in baseline characteristics between the 2 randomized arms. Compared to placebo, a lesser proportion of patients in the patisiran arm had the Val30Met variant (52% vs 38% respectively, $p<0.05$), and had more severe impairment as indicated by a 3.5 points higher mean neuropathy impairment score (NIS) score. Furthermore, there was a 14% absolute difference in the proportion of patients with cardiac involvement between the patisiran (61%) and placebo (47%) groups. These factors suggest the potential for imbalances in baseline disease severity and natural history between the 2 groups.

The results of the trial are summarized in Table 6. The trial met its primary endpoint. The proportion of responders was 56% in patisiran arm vs 4% in the placebo arm (odds ratio=39.9;

95% confidence interval; 11.0 to 144.4). Neuropathy-related QOL, measured by the Norfolk-QOL-DN, also improved significantly. Detailed analysis on QOL at 18 months reported that patisiran improved the Norfolk QOL-DN total score and three individual domains as well as COMPASS-31 total scores relative to baseline. (28) However, neither the mNIS+7 nor the Norfolk-QOL-DN has a validated threshold of what magnitude of improvement or worsening is clinically relevant. The effect of patisiran was consistent and statistically significant for other secondary endpoints.

Cardiac outcomes (global longitudinal strain, left ventricular wall thickness and N-terminal pro b-type natiuretic peptide [NT-pro-BNP] levels) were assessed in a prespecified cardiac subpopulation that included patients with a left ventricle wall thickness ≥13 mm at baseline and with an absence of a history of hypertension or aortic valve disease. Disproportionately more patisiran patients met these criteria compared to placebo patients (90 [61%] vs. 36 [47%], respectively). Furthermore, in the subset with cardiac involvement, patients in the placebo arm had more severe polyneuropathy (NIS score) and familial amyloid polyneuropathy (FAP) stage 2 while more patients in the patisiran group had New York Heart Association class II heart failure. Higher NT-pro-BNP levels have been shown to predict mortality in hATTR patients with cardiac involvement. (9) Among patisiran treated patients, NT-pro-BNP decreased by a median of 49.9 ng/L, while among placebo-treated patients, levels increased by a median of 320.4 ng/L, yielding a statistically significant treatment difference of 370.2 ($p<.0001$). However, the median NT-pro-BNP levels were below the 3000 ng/L cut-off associated with increased risk of death both at baseline and after treatment. (29) In post-hoc composite outcome analyses (data not shown), patients receiving patisiran also had a lower composite rate of cardiac hospitalization and/or all-cause mortality, as well as a lower composite rate of any hospitalization and/or all-cause mortality. However, the results did not report on all-cause mortality alone.

Open Label Extension (OLE) Studies

Data from an open-labeled extension (OLE) study (NCT02510261) of the APOLLO as well as a phase II study suggests a sustained delay of progression of polyneuropathy and maintenance of QOL. (30) The published findings of this study are based on the interim analysis of the patients who had completed 12-month efficacy assessments as of the data cutoff (Sep 24, 2018). Study participants received patisiran for a mean of 20.5 months (±8.0) and had a cumulative drug exposure of 359.6 patient-years. The rapid polyneuropathy progression observed among patients in the APOLLO-placebo group halted upon treatment with patisiran in the global OLE. However, the mean mNIS+7 score did not return to APOLLO baseline. Furthermore, neurological disability and mortality remained higher in APOLLO placebo patients compared to participants who received patisiran in the parent studies, underscoring the importance of treatment at the earliest disease stage possible. This report, however, is an interim analysis and continued observation and reporting are needed to assess whether the clinical benefits are maintained to the end of the 5-year global OLE.

Schmidt et al. (2022) reported the results of a single-arm open label study (NCT03862807) that enrolled 23 adults who had received a liver transplant for treatment of hATTR ≥12 months before study entry and had experienced polyneuropathy progression post-liver transplant.

(31) The primary endpoint was median transthyretin reduction from baseline. Twenty-three study participants received patisiran for 12 months alongside immunosuppression regimens. The mean TTR level (±standard error of the mean [SEM]) at baseline was 202.1 (±11.3) mg/l. Respective levels 3 weeks, 6-months and 12-months post treatment were 35.5 (±4.5), 21.2 (±3.7) and 24.9 (±2.7) which translates to mean (±SEM) percent reduction from baseline to 81.9% (±2.9), 89.2% (±2.0) and 87.1 (±1.7) respectively. Neuropathy, quality of life, and autonomic symptoms were assessed by measuring the change from baseline to month 12 in neuropathy impairment score, Norfolk quality of life-diabetic neuropathy questionnaire, and composite autonomic symptom score-31. Respective change was -3.7 (±2.7), -6.5 (±4.9) and -5.0 (±2.6). Adverse events were mild or moderate; 5 patients experienced ≥1 serious adverse event.

Table 5. Summary of Key RCT Characteristics: Patisiran

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Adams et al. (2018); APOLLO (NCT01960348) (27)	Multiple countries	14	2013-2016	235 adults (age 18 to 85 years) with hATTR with polyneuropathy, NIS scores ranging from 5 to 130, Karnofsky performance status ≥ 60%, PND score ≤IIIb, and anticipated survival of at least 2 years Primary outcome: Change in neurologic function (mNIS+7) after 18 months of treatment Responder definition: Less than 10-point increase from baseline in the mNIS+7 at 18 months Randomization stratified by previous TTR stabilizer use, NIS	n=148 patisiran 0.3 mg/kg IV Q3W for 18 months Cardiac subpopulation n=90	n=77 placebo IV Q3W for 18 months Cardiac subpopulation n=36

				score (5-49 vs 50-131), and early-onset disease defined as before age 50 in the presence of Val30MET variant vs. all other pathogenic variants, including late-onset disease in the presence of Val30Met		
Adams et al. (2021) (NCT02510261) (30) Interim results at 12 months	Multiple countries	56	2015-2017	211 adults who completed the phase 3 APOLLO or phase 2 OLE parent studies and tolerated the study drug As per protocol, the study does not have prespecified primary or secondary outcomes. Efficacy outcomes included mNIS+7, Norfolk QOL-DN, COMPASS-31, modified BMI, R-ODS, PND score, familial amyloid polyneuropathy stage, 10-m walk test, grip strength, and NT-proBNP concentrations	N=211 patisiran (APOLLO placebo =49; APOLLO n=137; phase 2 OLE=25) 0.3 mg/kg IV Q3W	None

BMI: body mass index; hATTR: hereditary transthyretin-mediated; IV: intravenous; kg: kilogram; mNIS+7: modified Neuropathy Impairment Score +7; NIS: Neuropathy Impairment Score; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OLE: open-label extension; PND: polyneuropathy disability; Q3W: every 3 weeks; QOL-DN: quality of life-diabetic neuropathy; R-ODS: Rasch-built overall disability scale; TTR, transthyretin.

Table 6. Summary of Key RCT Results: Patisiran

Study	LSM Difference (mNIS+7)	LSM Difference (Secondary Outcomes)	PND Score (Disease Progression), n (%)	LSM Difference (QOL)	Safety n (%)
Adams et al. (2018); APOLLO (27)					
N	235	235	203	235	235
Patisiran	-6.0±1.7	NIS-W: 0.1±1.3 R-ODS: 0.0±0.6 10-MWT[a]: 0.08±0.02 mBMI[b]: -3.7±9.6 COMPASS-31: -5.3±1.3	Improved: 12 (8) No Change: 96 (65) Worsened: 30 (20) Missing: 10 (7)[c]	Norfolk QOL: -6.7±1.8 EQ-5D-5L: 0.3±0.2 EQ-5D-VAS: -7.1±2.3	Any AE: 97% Any SAE: 36% AE Rx discontinuation: 5% AE trial withdrawal: 5%
Placebo	28.0±2.6	NIS-W: 17.9±2.0 R-ODS: -8.9±0.9 10-MWT[a]: -0.24±0.04 mBMI[b]: -119.4±14.5 COMPASS-31: 2.2±1.9	Improved: 0 No Change: 23 (30) Worsened: 32 (42) Missing: 22 (29)[c]	Norfolk QOL: 14.4±2.7 EQ-5D-5L: -0.17±0.02 EQ-5D-VAS: 2.4±1.6	Any AE: 97% Any SAE: 40% AE Rx discontinuation: 14% AE trial withdrawal: 12%
Diff (±SE)	-34±3.0	NIS-W: 17.9±2.3 R-ODS: 9.0±1.0 10-MWT[a]: 0.31±0.04	Not reported	Norfolk QOL: -21.1 EQ-5D-5L: 0.2 EQ-5D-VAS: 9.5	NA

		mBMI[b]: 115.7±16.9 COMPASS-31: -7.5±2.2			
P Value	<0.001	All p values: <0.001	Not reported	All p values: <0.001	NA
Adams et al. (2021) (30)	**Change in mean mNIS+7 (95% CI)**	**Norfolk QOL-DN**	**Safety (Serious adverse events)**		
APOLLO-patisiran	-4.0 (-7.7 to -0.3)[d]	-3.9 (-8.1 to 0.3)	48/137 (35%)		
Phase 2 OLE	-4.7 (-11.9 to 2.4)[d]	Not reported	6/25 (24%)		
APOLLO-placebo	-1.4 (-6.2 to 3.5)[d]	-4.5 (-9.6 to 0.7)	28/49 (57%)		

0-MWT: 10-meter walk test; AE: adverse event; CI: confidence interval; COMPASS-31: Composite Autonomic Symptom Score-31; EQ-5D-5L: Euro-QOL 5-dimension 5-level; EQ-VAS: Euro-QOL Visual Analogue Scale; LSM: least squares mean; mBMI: modified body mass index; mNIS+7: Modified Neuropathy Impairment Score; NIS-W: Neuropathy Impairment Score – Weakness; OLE: open label extension; PND: polyneuropathy disability; QOL: quality of life; QOL-DN: Quality of Life - Diabetic Neuropathy; R-ODS: Rasch-built-Overall Disability Scale; SE: standard error; SAE; serious adverse event

[a] meter/seconds.

[b] kilogram/meter^2 x albumin (gram/deciliter).

[c] Missing includes all deaths prior to 18-month visit.

[d] Change from parent study baseline.

The purpose of the study limitations tables (Table 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides conclusions on the sufficiency of evidence supporting the position statement. A gap in relevance for the APOLLO trial is related to the generalizability of its results to the U.S. population. Only 20% of APOLLO participants were from the U.S. and included only 2 patients (0.9%) with the Val122Ile variant, which is the most common variant observed in the U.S. This was likely due to the trial inclusion criterion of polyneuropathy-predominant hATTR. Secondly, while the OLE phase of the study has reported outcomes data up to 12 months, long-term safety data is inadequate as these drugs are intended for chronic use. In addition to these limitations, the impact of statistically significant imbalances, potentially clinically relevant differences in baseline characteristics, and a higher rate of trial discontinuation in the placebo arm vs patisiran arm in the APOLLO trial is unclear. No major gaps were identified in study design and conduct except in the open label extension study, since there could be selection bias as the population for this study was self-selected from previous patisiran studies.

Table 7. Study Relevance Limitations: Patisiran

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Adams et al. (2018); APOLLO (27)	4. Study population not representative of intended use.				1, 2. 36-months follow-up is insufficient to establish long-term harms.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Summary of Evidence

For individuals who are adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) who receive patisiran, the evidence includes 1 pivotal randomized controlled trial (RCT). Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life (QOL), treatment-related morbidity, and treatment-related mortality. Data from the APOLLO III trial demonstrated a statistically significant mean improvement in neurologic function and neuropathy-related QOL with patisiran at 18 months compared to placebo. Post-hoc evidence also suggests a decreased risk of the composite endpoint of all-cause mortality and hospitalization among those with cardiac involvement. However, results of APOLLO trial have limited generalizability because only 20% of APOLLO participants were from the U.S. and included only 2 participants (0.9%) with Val122Ile variant, which is the most common variant observed in the U.S. There is also uncertainty regarding long-term benefits and harms for a treatment that is intended to be used lifelong. Studies on long-term safety and tolerability are ongoing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

No guidelines or statements from U.S. societies were identified.

Consensus Statements from European Network for Transthyretin-Mediated Amyloidosis-Familial Amyloid Polyneuropathy

Consensus statements from the European Network (2016) for transthyretin-mediated amyloidosis-familial amyloid polyneuropathy were published prior to the approval of patisiran and inotersen and, therefore, do not include any recommendation for either of the drugs.

(32) These guidelines recommend that following a clinical suspicion, positive results from both biopsy and genetic analysis are essential to distinguish transthyretin-mediated amyloidosis-familial amyloid polyneuropathy from a large number of peripheral neuropathies.

National Institute for Health and Care Excellence (NICE)
On August 14, 2019, the NICE issued highly specialized technologies guidance on patisiran for treating hereditary transthyretin amyloidosis. Patisiran is recommended, within its marketing authorization, as an option for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy. It is recommended only if the company provides patisiran according to the commercial arrangement. (33)

Institute for Clinical and Economic Review (ICER)
The ICER (2018) published a Report on comparative effectiveness and value of inotersen and patisiran for hereditary transthyretin-mediated amyloidosis. (11) Differences in the primary outcome measures and trial population (e.g., race, geographic region, disease severity) precluded a direct comparison of the Phase III APOLLO; (patisiran) and NEURO-TTR (inotersen) trials. Using criteria from the U.S. Preventive Services Task Force, the authors of the ICER rated the APOLLO trial to be of fair quality due to differential drop-out between treatment groups and the NEURO-TTR trial to be of fair quality based on baseline differences in autonomic and sensorimotor neuropathy severity between treatment groups.

In summarizing the clinical evidence, the ICER Report noted, “In considering the current evidence for inotersen and patisiran, the limitations of inotersen and patisiran clinical evidence include study populations that limit the generalizability of clinical outcomes to all hATTR patients, clinical outcome measures (mNIS+7 and Norfolk-QOL-DN) without defined thresholds for clinical significance, limited functional outcomes such as disease stage progression, and limited data on patients with cardiac involvement, especially among cardiac-dominant patients who are at a higher risk for mortality than patients with neuropathy-predominant hATTR.” Further, they also noted, “there may be uncertainties related to the translation of neurologic outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications.”

The Report concluded that for patisiran, there is moderate certainty of a substantial net health benefit with a high certainty of at least a small net health benefit compared to best supportive care, and therefore rated the clinical evidence for patisiran to be incremental or better (“B+”).

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 8.

Table 8. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03997383[a]	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy)	360	Jun 2025
NCT04561518[a]	ConTTRibute: A Global Observational Study of Patients With Transthyretin (TTR)-Mediated Amyloidosis (ATTR Amyloidosis)	1500	Sep 2030
NCT05873868	Myocardial Effects in Patients With hATTR With Polyneuropathy Treated With Patisiran (MyocardON-TTR)	20	Jul 2024

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0222

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/31/2025	Document became inactive.
02/01/2025	Document updated with literature review. The following change was made to Coverage: Updated examples of other transthyretin reducing agents that should not be used in combination with Onpattro® (patisiran), under both initial and continuation therapy sections. Added references 18-26 and 31-33.
12/01/2023	Reviewed. No changes.
03/01/2023	Document updated with literature review. The following change was made to Coverage: Revised the statements under both Initial Therapy and Continuation Therapy regarding combined use of other transthyretin (TTR) reducing agents and included vutrisiran in the listing. Added references 23, 24; some revised, others removed.
04/15/2021	Document updated with literature review. Coverage unchanged. Added references 4-19 and 21-24.
12/15/2020	Reviewed. No changes.
12/01/2019	New medical document. Onpattro™ (patisiran) may be considered medically necessary for adult patients with a confirmatory diagnosis of hereditary transthyretin-mediated amyloidosis who meet criteria. Onpattro™ (patisiran) is considered experimental, investigational and/or unproven in all other situations. NOTE 1: Authorization approval duration (initial and reauthorization): 12 months.