Treatment of Hereditary Transthyretin-Mediated Amyloidosis in Adult Patients

Policy # 00670
Original Effective Date: 04/24/2019
Current Effective Date: 07/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: tafamidis products (Vyndaqel®, Vyndamax™) for the treatment of cardiomyopathy of transthyretin-mediated amyloidosis are addressed separately in medical policy 00694.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider patisiran (Onpattro™)‡, vutrisiran (Amvuttra™)‡, inotersen (Tegsedi™)‡, or eplontersen (Wainua™)‡ for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for patisiran (Onpattro), vutrisiran (Amvuttra), inotersen (Tegsedi), or eplontersen (Wainua) will be considered when the following criteria are met:

- Initial therapy:
    - Patient has a diagnosis of hereditary transthyretin amyloidosis (hATTR) confirmed by BOTH of the following:
        - Genetic test positive for a mutation to the transthyretin (TTR) gene that is pathogenic or likely pathogenic; AND
        - Signs and symptoms consistent with the polyneuropathy of hATTR amyloidosis including any of the following:
            - Peripheral sensorimotor polyneuropathy [e.g., impaired sensation (e.g. pain, temperature, vibration, touch, tingling), reduced motor strength/coordination, difficulty walking]; OR

- ❖ Autonomic neuropathy symptoms [e.g., orthostatic hypotension, abnormal sweating, dysautonomia (constipation and/or diarrhea, nausea, vomiting, early satiety, bladder dysfunction)]; AND
- Patient has clinical signs and symptoms of polyneuropathy characterized by ONE of the following:
  - Baseline polyneuropathy disability (PND) score of I, II, IIIa, or IIIb; OR
  - Baseline familial amyloid polyneuropathy (FAP) stage one or two; AND
- Documentation is provided of the patient's baseline PND score OR FAP stage; AND *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is 18 years of age or older; AND
- Patient does NOT have any of the following:
  - Prior liver transplantation; OR
  - New York Heart Association (NYHA) class III or IV heart failure; OR
  - Sensorimotor or autonomic neuropathy not related to hATTR (e.g., monoclonal gammopathy, autoimmune disease); AND
    *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
- If the request is for Onpattro, the dose will not exceed 30 mg every 3 weeks; AND
- If the request is for Amvuttra, the dose will not exceed 25 mg every 3 months; AND
- Onpattro, Tegsedi, Amvuttra, or Wainua will not be used in combination; AND
- Requested drug will NOT be used in combination with a tafamidis product (Vyndaqel®‡ or Vyndamax™‡).

- Continuation therapy:
  - Patient has received an initial authorization for the requested drug; AND
  - Patient's PND stage or FAP score remains stable or improved compared to baseline; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Onpattro, Tegsedi, Amvuttra, or Wainua will not be used in combination; AND

- Patient has NOT had prior liver transplantation; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Requested drug will NOT be used in combination with a tafamidis product (Vyndaqel or Vyndamax).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of patisiran (Onpattro), vutrisiran (Amvuttra), inotersen (Tegsedi), or eplontersen (Wainua) when no documentation of PND score or FAP stage is provided; when the patient has had prior liver transplantation, heart failure, or neuropathy not related to hATTR to be **not medically necessary.****

Based on review of available data, the Company considers the continuation of patisiran (Onpattro), vutrisiran (Amvuttra), inotersen (Tegsedi), or eplontersen (Wainua) when the PND or FAP score has not remained stable or improved on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of patisiran (Onpattro), vutrisiran (Amvuttra), inotersen (Tegsedi), or eplontersen (Wainua) when patient selection criteria are not met (except for those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Onpattro, Tegsedi, Amvuttra, and Wainua are approved in the United States for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults. Despite their similar indications, these drugs differ in mechanism of action, route of administration, and adverse effect profile.

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Onpattro is a small interfering ribonucleic acid (siRNA) which is designed to selectively target variant and wild-type transthyretin mRNA through RNA interference. This results in a reduction of serum transthyretin (TTR) and TTR deposits in tissues. Onpattro should be administered via intravenous infusion by a healthcare professional once every three weeks. For patients less than 100 kg, the dose should be 0.3 mg/kg every 3 weeks, and for patients weighing 100 kg or more, the dose should be 30 mg every 3 weeks. To reduce the risk of infusion-related reactions, patients should be premedicated with a corticosteroid, acetaminophen, H1 blocker, and H2 blocker 60 minutes prior to infusion.

Amvuttra is also a siRNA targeting transthyretin mRNA to reduce serum TTR and TTR deposits in tissues. Unlike Onpattro, Amvuttra is administered via SC injection once every 3 months by a healthcare professional. The recommended dosage is 25 mg every 3 months regardless of the patient's weight.

Tegsedi is an antisense oligonucleotide that causes degradation of variant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR and TTR deposits in tissues. Tegsedi should be administered via subcutaneous injection of 284 mg once weekly. Because it causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, Tegsedi is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. In addition, patients must have a platelet count of at least 100 x 10^9/L and no history of acute glomerulonephritis caused by Tegsedi in order to receive treatment. Prior to treatment, platelet count, alanine amino transferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and urinalysis should be obtained. During treatment, SCr, eGFR, urinalysis, and UPCR should be monitored every 2 weeks and ALT, AST, and total bilirubin should be measured every 4 months. The FDA-approved package labeling provides guidance for adjusting or holding the dose based on the results of these tests.

Wainua is an anti-sense oligoneucleotide-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The recommended dosage of Wainua is 45 mg administered by subcutaneous injection once monthly. Wainua may be self-administered or administered by a caregiver.

All of these drugs cause a decrease in serum vitamin A levels and therefore vitamin A supplementation at the recommended daily allowance is advised. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Hereditary Transthyretin-Mediated Amyloidosis (hATTR)
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. Variance in the transthyretin gene results in the production of misfolded transthyretin protein which is insoluble and accumulates as amyloid fibrils (i.e., amyloidosis) in multiple organs of the body causing disruption of organ tissue structure and function. 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 US. It is estimated that the neuropathy-predominant form of hATTR affects at least 10,000 people worldwide, and roughly 3,000-3,500 people in the US. Due to under-diagnosis and a lack of population-based data, these numbers may underestimate the actual prevalence.

Historically, hATTR was classified into two distinct syndromes—amyloidosis with polyneuropathy (previously known as familial amyloid polyneuropathy or FAP) and amyloidosis with cardiomyopathy (previously known as familial amyloid cardiomyopathy or FAC). 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, current clinical approach treats FAP and FAC as one hereditary disease with a spectrum of clinical manifestations. The first symptoms of hATTR amyloidosis typically appear between the mid-20s and 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. While the neurologic symptoms of hATTR are among the most physically disabling, cardiac manifestations are most predictive of early death. Cardiac manifestations include arrhythmias, conduction disorders, cardiomegaly, and heart failure. If the disease is untreated, median survival for patients with predominantly neuropathic symptoms is 5-15

years, while patients with predominantly cardiomyopathic symptoms have a median survival of 2.5-6 years.

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. Further, age of onset and rate of progression are highly variable from patient to patient. As a result, many patients are misdiagnosed or diagnosis is delayed and patients often see physicians across multiple specialties before receiving an accurate diagnosis. To confirm diagnosis, proven amyloid deposition in biopsy specimens and identification of a pathogenic variant in transthyretin gene are necessary. Sequence analysis of the transthyretin gene, the only gene in which mutation is known to cause hATTR, detects more than 99% of pathogenic variants.

The Familial Amyloid Polyneuropathy (FAP) stage system and the polyneuropathy disability (PND) score are the two most commonly 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 hATTR

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

Prior to the approval of Onpattro, Tegsedi, Amvuttra, and Wainua there was no FDA-approved treatment available in the US for the treatment of hATTR. Management approaches include the use of pharmacotherapy with tetramer stabilizers (such as diflunisal and tafamidis) and surgery (orthotopic liver transplant). Diflunisal is a generic nonsteroidal anti-inflammatory drug that is not approved by the FDA for the treatment of hATTR but is available in the US as a generic and is used off-label. It has been shown to stabilize transthyretin tetramers in a phase I study and 1 randomized controlled trial, but the adverse effects of gastrointestinal bleeding, worsening renal insufficiency, and cardiovascular events preclude its long-term use. Tafamidis is a tetramer stabilizer that is available in the European Union and several South American and Asian countries, but has not yet been approved for the treatment of polyneuropathy associated with hATTR in the US.

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 life-long immunosuppression, and reports of disease progression following liver transplantation limit its use. Further, orthotopic liver transplantation is not recommended for patients with cardiac involvement due to the observed post-transplant progression of cardiac symptoms.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Onpattro was approved in August 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Tegsedi was approved in October 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Amvuttra was approved in June 2022 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Wainua was approved in December 2023 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Onpattro

The efficacy of Onpattro was established in one pivotal randomized controlled trial (APOLLO) that included 225 adults with hATTR with polyneuropathy. These patients were randomized to receive either Onpattro or placebo. Change in neurologic function using the mNIS+7 was the primary outcome after 18 months of treatment. The mNIS+7 scale was designed to assess both small and large fiber impairment in hATTR clinical trials and has a total score of 304-346.6 points with higher scores indicating worsening disease and disability. Randomization was stratified based by previous TTR stabilizer use, NIS score, and early-onset disease defined as before age 50 in the presence of Val30Met variant versus all other pathogenic variants, including late-onset disease in presence of Val30Met. However, there were several differences in baseline characteristics between the two randomized arms. Compared to placebo, a lesser proportion of patients in the Onpattro arm had the Val30Met variant (52% vs 38%) and also had more severe impairment as indicated by 3.5 points higher mean NIS score. Further, there was a 14% absolute difference in the proportion of patients with cardiac involvement between the Onpattro (61%) and placebo (47%) groups. These factors suggest the potential for imbalances in baseline disease severity and natural history between the two groups.

The primary outcome of least square mean (LSM) change from baseline to 18 months in mNIS+7 significantly favored Onpattro compared with placebo, with a treatment difference of -34.0 ($p<0.001$). The proportion of patients classified as responders by achieving a negative mNIS+7 change from baseline was 56% in the Onpattro arm versus 4% in the placebo arm (OR=39.9; 95% CI: 11-144.4). Neuropathy-related quality of life (QOL), measured by the Norfolk-QOL-DN also improved significantly, but the difference was driven by worsening scores in the placebo arm and only modest improvements in three neuropathy domains in the Onpattro arm. However, neither the mNIS+7 nor the Norfolk-QOL-DN have a validated threshold of what magnitude of improvement

or worsening is clinically relevant. The effect of Onpattro was consistent and statistically significant on other secondary endpoints.

Cardiac outcomes (global longitudinal strain, left ventricular wall thickness and NT-proBNP levels) were assessed in a pre-specified cardiac subpopulation that included patients with a left ventricle wall thickness >13 mm at baseline and absence of a history of hypertension or aortic valve disease. Disproportionately more Onpattro patients met these criteria compared to placebo patients (90 [61%] vs. 36 [47%], respectively). Further, in the subset with cardiac involvement, patients in the placebo arm had more severe polyneuropathy (NIS score) and FAP stage II while more patients in the Onpattro group had NYHA class II heart failure. Higher NT-pro-BNP levels have been shown to predict mortality in hATTR patients with cardiac involvement. Among Onpattro treated patients, NT-pro-BNP decreased by a median of 49.9 mg/dL while among placebo treated patients, they increased by a median of 320.4 ng/L yielding a treatment difference of 370.2 which was statistically significant ($p<0.0001$). However, the median NT-pro-BNP levels were below the 3,000 ng/L cut-off associated with increased risk of death both at baseline and after treatment. In a post-hoc composite outcome analysis, patients receiving Onpattro 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, results did not report on all-cause mortality alone.

Data from open labeled extension studies of the APOLLO trial suggest sustained delay of progression of polyneuropathy after 24 months and 36 months of follow-up. Cardiac endpoints did not differ statistically between the Onpattro group and the placebo group after 15 months of intervention; however, the trial was not powered to detect differences in cardiac outcomes.

A gap in relevance for the APOLLO trial is related to generalizability of its results to the US population. Only 20% of the APOLLO participants were from the US and included only 2 patients (0.9%) with Val122IIe variant, which is the most common variant observed in the US. This was likely due to the trial inclusion criterion of polyneuropathy-predominant hATTR. Secondly, while the open-labeled extension phase of the study has report outcomes data up to 36 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 and potentially clinically relevant differences in baseline characteristics and a higher rate of trial discontinuation in the placebo arm vs Onpattro arm in unclear.

Tegsedi
The efficacy of Tegsedi was determined in one pivotal, randomized controlled trial (NEURO-TTR) with 172 adults with hATTR amyloidosis with polyneuropathy. The patients were randomized to receive either Tegsedi or placebo. Change in neurologic function using the mNIS+7 and Norfolk QOL-DN were the co-primary outcomes after 15 months of treatment. Randomization was stratified by disease stage (FAP Stage 1 vs 2), TTR mutation (Val30Met vs. non-Val30Met) and prior use of TTR stabilizers (tafamidis and/or diflunisal). Although the treatment arms were well balanced at baseline, notable imbalances included more severe sensorimotor and autonomic neuropathy and higher proportion of patients with cardiac symptoms in the Tegsedi group compared to placebo.

The primary outcome of LSM change from baseline to 15 months in mNIS+7 significantly favored Tegsedi compared to placebo with a treatment difference of -19.7 points ($p<0.001$). However, the mNIS+7 used in this trial was substantially different from the mNIS+7 used in the APOLLO trial. Unlike the mNIS+7 used in the APOLLO trial in which the maximum possible score was 304 points in 5 domains (motor strength, reflexes, quantitative score testing, nerve conduction testing and postural blood pressure), mNIS+7 used in the NEURO-TTR trial the maximum possible score was 346.6 points with 6 domains (motor strength, reflexes, sensation, quantitative score testing, nerve conduction testing, and heart rate response to deep breathing). Tegsedi treatment also improved neuropathy-related quality of life as shown by improvement in mean scores as well as proportion of patients reporting improved scores after 15 months of treatment with Tegsedi compared to those on placebo. However, neither the mNIS+7 nor the Norfolk-QOL-DN have a validated threshold of what magnitude of improvement or worsening is clinically relevant. Cardiac endpoints did not differ statistically between the Tegsedi group and the placebo group after 15 months of interventions; however, the trial was not powered to detect differences in cardiac outcomes.

Cardiac outcomes (global longitudinal strain or other echocardiographic measures, including ejection fraction, posterior wall thickness, and left ventricular mass) were assessed in a cardiac subpopulation that included patients with intraventricular septum thickness >1.3 cm. There was no evidence of improvement in cardiac outcomes with Tegsedi after 15 months compared to placebo.

Tegsedi was approved with a black box warning because it can cause sudden and unpredictable thrombocytopenia that can be life-threatening. Platelet counts below 100 x 10^9/L occurred in 25% of Tegsedi-treated patients compared with 2% of patients on placebo. Platelet counts below 75 x 10^9/L occurred in 14% of Tegsedi-treated patients, compared to no patient on placebo. In the

NEURO-TTR trial and its extension study, 39% of Tegsedi-treated patients with a baseline platelet count below 200 x 10^9/L had a nadir platelet count below 75 x 10^9/L, compared to 6% of patients with a baseline platelet count 200 x 10^9/L or higher. Three Tegsedi-treated patients had sudden severe thrombocytopenia (platelet count below 25 x 10^9/L), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One patient in a clinical trial experienced a fatal intracranial hemorrhage.

A gap in relevance for NEURO-TTR trial is related to generalizability of its results to the US population. Only 3 patients (1.7%) were included with a Val122IIe variant, which is the most common variant observed in the US. This was likely due to the trial exclusion criterion of polyneuropathy-predominant hATTR. Secondly, while the open-labeled extension phase of the study has reported outcomes data up to 52 months, long-term safety data is inadequate as these drugs are intended for chronic use. Lastly, treatment discontinuations occurred more frequently among Tegsedi patients compared to placebo (22.3% vs 13.3%). Tegsedi patients discontinued most commonly due to adverse effects while placebo patients discontinued most commonly due to voluntary withdrawal and disease progression.

Amvuttra
The efficacy of Amvuttra was evaluated in a randomized, open-label clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis. Patients were randomized 3:1 to receive 25 mg of Amvuttra subcutaneously once every 3 months (n=122) or 0.3 mg/kg Onpattro intravenously every 3 weeks (n=42) as a reference group. Efficacy assessments were based on a comparison of the Amvuttra arm of this study with an external placebo group in another study composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis. The primary efficacy endpoint was the change from baseline to Month 9 in modified Neuropathy Impairment Score +7 (mNIS+7). The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified+7 composite scores. In the version of the mNIS+7 used in the trial, the NIS objectively measures deficits in cranial nerve function, muscle strength, and reflexes, and the +7 assesses postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The mNIS+7 has a total score range from 0 to 304 points, with higher scores representing a greater severity of disease. Treatment with Amvuttra in this study resulted in statistically significant improvements in the mNIS+7 at Month 9 compared to placebo in the external study ($p<0.001$) with a change from baseline of -2.2 in the Amvuttra group and 14.8 in the placebo group.

Wainua
The efficacy of Wainua was demonstrated in a randomized, open-label, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis. Patients were randomized in a 6:1 ratio to receive either 45 mg of Wainua once every 4 weeks (n=144) or 284 mg of inotersen once per week (n=24), respectively, as subcutaneous injections. Efficacy assessments were based on a comparison of the Wainua arm of Study 1 with an external placebo group (n=60) in another study composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis. The efficacy endpoints were the change from baseline to Week 35 in the mNIS+7 composite score and the change from baseline to Week 35 in the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) total score. The validated version of the mNIS+7 score used in the trial has a range of -22.3 to 346.3 points, with higher scores representing a greater severity of disease. The version of the Norfolk QOL-DN that was used in the trial has a range from -4 to 136 points, with higher scores representing greater impairment.

Treatment with Wainua resulted in statistically significant improvements in the mNIS+7 and the Norfolk QOL-DN total scores, compared to the external placebo control ($p<0.001$) at Week 35. The baseline mNIS+7 score was 79.6 for the Wainua group and 74.1 for the placebo group. At Week 35, the score had increased by 0.2 points in the Wainua group and 9.2 points in the placebo group. This translated to a treatment difference of -9.0 (95% CI: -13.5, -4.5, $p<0.001$). The baseline Norfolk QOL-DN score was 43.5 for the Wainua group and 48.6 for the placebo group. At Week 35, the score had decreased by 3.1 points in the Wainua group and increased 8.7 points in the placebo group. This translated to a treatment difference of -11.8 (95% CI: -16.8, -6.8, $p<0.001$).

References

1. Coelho T, Maurer MS, Suhr OB. THAOS- The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin. Jan 2013;29(1):63-76
2. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. Jun 2017;23(7 Suppl):S107-S112.
3. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. J Am Coll Cardiol. Dec 1 2015;66(21):2451-2466.
4. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. Feb 2013;8:31.

5. Arvanitis M, Chan GG, Jacobson DR, et al. Prevalence of mutant ATTR cardiac amyloidosis in elderly African Americans with heart failure. Amyloid. Dec 2017;24(4):253-255.
6. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. Feb 2016;29 Suppl 1:S3-S13.
7. Sekijima Y, Yoshida K, Tokuda T, et al. Familial Transthyretin Amyloidosis. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA)1993.
8. 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. Sep 11 2017;17(1):181.
9. Suanprasert N, Berk JL, Benson MD, et al. Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials. J Neurol Sci. Sep 15 2014;344(1-2):121-128.
10. Solomon SD, Adams D, Kristen A, et al. Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients with Hereditary Transthyretin-Mediated Amyloidosis: An Analysis of the APOLLO Study. Circulation.0(0).
11. Klaassen SHC, Tromp J, Nienhuis HLA, et al. Frequency of and Prognostic Significance of Cardiac Involvement at Presentation in Hereditary Transthyretin-Derived Amyloidosis and the Value of N-Terminal Pro-B-Type Natriuretic Peptide. Am J Cardiol. Jan 1 2018;121(1):107-112.
12. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. Jul 5 2018;379(1):22-31.
13. Amvuttra [package insert]. Alnylam Pharmaceuticals, Inc., Cambridge, MA. Updated June 2022.
14. Amvuttra (vutrisiran) New Drug Review. IPD Analytics. June 2022.
15. Wainua [package insert]. AstraZeneca Pharmaceuticals LP. Wilmington, DE. Updated December 2023.

Policy History

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04/04/2019 Medical Policy Committee review
04/24/2019 Medical Policy Implementation Committee approval. New policy.
08/12/2019 Coding update
10/03/2019 Medical Policy Committee review

10/09/2019 Medical Policy Implementation Committee approval. Coverage changes to add criteria to include both initial and continuation therapy: "Requested drug will NOT be used in combination with a tafamidis product (Vyndaqel or Vyndamax).
10/01/2020 Medical Policy Committee review
10/07/2020 Medical Policy Implementation Committee approval. No change to coverage.
10/07/2021 Medical Policy Committee review
10/13/2021 Medical Policy Implementation Committee approval. No change to coverage.
10/06/2022 Medical Policy Committee review
10/11/2022 Medical Policy Implementation Committee approval. No change to coverage.
12/01/2022 Medical Policy Committee review
12/14/2022 Medical Policy Implementation Committee approval. Added new drug, Amvuttra, to policy with relevant background information.
12/07/2023 Medical Policy Committee review
12/13/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2024 Medical Policy Committee review
06/12/2024 Medical Policy Implementation Committee approval. Added new drug, Wainua, to policy with relevant criteria and background information.

Next Scheduled Review Date: 06/2025

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J0222, J0225, J3490
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

Treatment of Hereditary Transthyretin-Mediated Amyloidosis in Adult Patients

Policy # 00670
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Current Effective Date: 07/08/2024

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.