Original Effective Date: 12/08/2022
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Last P&T Approval/Version: 10/26/2022
Next Review Due By: 10/2023
Policy Number: C24213-A

Amvuttra (Vutrisiran)

PRODUCTS AFFECTED

Amvuttra (Vutrisiran)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):
1. Documentation of BOTH of the following:
   (a) pathogenic transthyretin (TTR) mutation verified by genetic testing
   Note: More than 120 different transthyretin (TTR) gene mutations have been identified, with predominant symptom presentation varying by genotype. The most common mutations in the US are V122I, T60A, and V30M
   AND

(b) ONE of the following: Polyneuropathy disability (PND) score ≤ IIIb, Familial amyloidotic polyneuropathy (FAP) stage 1 or 2 OR Neuropathy impairment score (NIS) between 10 and 130 [DOCUMENTATION REQUIRED]
AND

2. Documentation of presence of clinical signs and symptoms of the disease such as: Peripheral sensory-motor neuropathy (e.g., neuropathic pain, paresthesia, weakness, bilateral carpal tunnel syndrome, difficulty walking), Autonomic neuropathy (e.g., hypotension, recurrent urinary tract infections, sexual dysfunction, sweating abnormalities, urinary retention), Gastrointestinal manifestations (e.g., diarrhea, nausea, vomiting, unintentional weight loss), Cardiovascular manifestations (e.g., arrhythmias, conduction abnormalities, heart failure)
AND
3. The member has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin- type product (e.g., gabapentin [Neurontin], Lyrica [pregabalin capsules]) or a tricyclic antidepressant (e.g., amitriptyline, nortriptyline), or Serotonin/Norepinephrine Reuptake Inhibitors (e.g., duloxetine)
AND
4. Prescriber attestation that member does NOT have ANY of the following conditions: New York Heart Association (NYHA) class III or IV heart failure; OR History of liver transplantation
AND
5. Prescriber attests member will not receive Amvuttra in combination with TTR-lowering agent, including Tegsedi and Onpattro OR TTR-stabilizing agent, including diflunisal, Vyndael, Vyndamax
AND
6. Prescriber attestation that member has been counseled on need for Vitamin A supplementation during therapy

CONTINUATION OF THERAPY:

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):
   1. Documentation of a positive response to therapy (e.g., improved neurologic impairment, motor function, slowing of disease progression, cardiac parameters, improvement in baseline scores: Polyneuropathy disability (PND) score ≤ IIIb OR FAP Stage 1 or 2, neuropathy impairment score) [DOCUMENTATION REQUIRED]
   AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age or older

QUANTITY:
25mg/0.5 mL single-dose prefilled syringe every 3 months

PLACE OF ADMINISTRATION:

Drug and Biologic Coverage Criteria

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous injection

DRUG CLASS:
Small interfering ribonucleic acid (siRNA)

FDA-APPROVED USES:
Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

The polyneuropathy disability score is an additional assessment tool with ranking based on different classes I-IV. Higher scores are indicative of more impaired walking ability. The varying classes are defined as follows:
I: preserved walking, sensory disturbances
II: impaired walking without need for a stick or crutches IIIa: walking with one stick or crutch IIIb: walking with two sticks or crutches

Familial Amyloid Polyneuropathy (FAP) clinical staging:
Stage 0: no symptoms
Stage 1: unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
Stage 2: assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
Stage 3: wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all Limbs

A. Scoring Scale of mNIS+7 (the higher the score, the less function)

A) mNIS+7

Test	Component	Minimum Score	Maximum Score
NIS	Cranial Nerves	0	40
	Muscle Weakness	0	152
	Reflexes	0	20
	Sensation	0	32
Modified +7	Heart Rate Deep Breathing+	-3.72	3.72
	Nerve Conduction+	-18.6	18.6
	Touch Pressure	0	40
	Heat-Pain	0	40
mNIS+7	**Composite**	**-22.3**	**346.3**

B. Scoring Scale of Norfolk QoL-DN (the higher the score, the poorer the quality of life)

B) Norfolk QoL-DN

Domain	Items[1,2]	Minimum Score	Maximum Score
Symptoms	∑ (1-9,9)	0	32
Physical Functioning/Large Fiber Neuropathy	∑ (8, 11, 13-15, 24, 27-35)	-4	56
Small Fiber Neuropathy	∑ (10, 16-18)	0	16
Large Fiber Neuropathy	∑ (19-21)	0	12
Activities of Daily Living	∑ (12, 22, 23, 25, 26)	0	20
Norfolk QoL-DN	**Total**	**-4**	**136**

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare condition affecting about 50,000 people worldwide caused by a genetic mutation in the transthyretin (TTR) gene. Mutations in the TTR gene lead to de-stabilization, misfolding and aggregation into insoluble amyloid fibrils which deposit into multiple sites such as the nervous system, heart, kidneys, and eyes. There are multiple TTR mutations, the most prevalent being TTR V30M. Common symptoms of hATTR amyloidosis include peripheral sensory or autonomic neuropathy, cardiomyopathy, and GI dysfunction. As the disease progresses, symptoms can worsen and lead to life-threatening multiorgan dysfunction.

Hereditary transthyretin-mediated amyloidosis manifests as abnormal buildup of amyloids which are protein fibers that deposit in organs and tissues in consequence interfering with normal functioning. The amyloid deposits usually occur in the peripheral nervous system, which can result in a loss of sensation, pain, or immobility in the arms, legs, hands and feet. They can also deposit in heart, kidneys, eyes and gastrointestinal tract and affect their functioning. The focus of the hATTR treatment is generally symptom management.

Given the magnitude of non-specific symptoms, diagnosis of hATTR is often challenging and is commonly confused with other conditions. Treatment options include liver transplantation and a limited number of pharmacologic therapies. While liver transplantation has been shown to eliminate the production of variant TTR protein and slow disease progression, it does not prevent cardiomyopathy as amyloids can continue to deposit in the heart. One treatment option is Vyndaqel (tafamidis), a transthyretin stabilizer, which stabilizes the tetramer of the TTR transport protein to slow the dissociation into monomers that drives TTR amyloidosis. Vyndaqel is indicated for the treatment of cardiomyopathy of wild type or hATTR amyloidosis. Recently approved treatment options for polyneuropathy of hATTR amyloidosis involve inhibition of hepatic production of TTR using a gene silencing RNA molecule, Onpattro (patisiran), Amvuttra (Vutrisiran) and an antisense oligonucleotide, Tegsedi (inotersen).

Amvuttra is a small interfering ribonucleic acid (siRNA) which works by silencing a portion of RNA involved in causing polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults. More specifically, Amvuttra prevents production of transthyretin (TTR) which leads to reduction in accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients better manage the condition. The FDA approval of Amvuttra is based on positive 9-month results from the Phase 3 HELIOS-A study (NCT03759379), a randomized, open-label, multicenter study of patients with hATTR-PN. The efficacy of Amvuttra was assessed by comparing the Amvuttra group in the HELIOS-A study with the placebo group from the Phase 3 APOLLO study of Onpattro. The primary endpoint was the change at 18 months from baseline to month 9 in the mNIS+7, an objective assessment of neuropathy that measures deficits in cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory

testing, and peripheral nerve electrophysiology. Participants aged 18-85 years were randomized 3:1 to receive one of the following for 18 months; 25mg of vutrisiran (n=122) via SC once every 3 months or 0.3mg/kg of patisiran (n=42) via IV infusion once every 3 weeks (reference group). The placebo cohort from the APOLLO study of Onpattro (n=77) was used as an external control for this study, in which patients received an IV infusion once every 3 weeks. At 9 months, Amvuttra met the trial's primary endpoint, with patients treated with the drug showing improvement with a 2.2 point mean decrease in mNIS+7 score from baseline, compared with a 14.8-point mean increase in mNIS+7 score in patients in the external placebo group, demonstrating a worsening of the condition at 9 months. Most common adverse reactions (>5%) were arthralgia, dyspnea, and Vitamin A decrease.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Amvuttra (Vutrisiran) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Amvuttra (Vutrisiran) include: No labeled contraindications.

Amvuttra has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions (coverage is not recommended for the following circumstances): NYHA heart failure classification >2, Primary or leptomeningeal amyloidosis, Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis or Concurrent use with of TTR-lowering agent, including Tegsedi and Onpattro OR TTR-stabilizing agent, including diflunisal, Vyndaqel, Vyndamax.

OTHER SPECIAL CONSIDERATIONS:
AMVUTTRA is for subcutaneous use only and should be administered by a healthcare professional. Amvuttra can lead to reduced serum vitamin A levels, vitamin A supplementation is advised if patient is taking Amvuttra. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. Amvuttra has not been studied in patients with severe renal or hepatic impairment.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J3490	**Unclassified drugs**

AVAILABLE DOSAGE FORMS:
Amvuttra SOSY 25MG/0.5ML single-dose prefilled syringe (in a carton containing one single dose)

REFERENCES

1. Amvuttra [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals. June 2022.
2. Rowczenio DM, Noor I, Gillmore JD, et al. Human Mutat. 2014;35(9):E2403-E2412.
3. Commissioner, Office of the. FDA Approves First-of-Its Kind Targeted RNA-Based Therapy to Treat a Rare Disease. U.S. Food and Drug Administration, FDA [online].
4. Adams D, Tournev IL, Taylor MS, et all., HELIOS-A Collaborators. Efficacy and Safety of vutirisan for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2022 Jul 23:1-9. doi: 10.1080/13506129.2022.2091985.
5. Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. Ther Adv

NeurolDisord. 2013 Mar; 6(2): 129–139
6. Institute for Clinical and Economic Review: Draft Evidence Report – Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. July 20, 2018.
7. Koike H, Tanaka F, Hashimoto R, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. J Neurol Neurosurg Psychiatry.2012 Feb;83(2):152-8.
8. Ando, Y., Coelho, T., Berk, J. L., Cruz, M. W., Ericzon, B. G., Ikeda, S., N Salvi, F. (2013). Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet journal of rare diseases*, *8*, 31. Doi:10.1186/1750-1172-8-31
9. Gales, L. (2019). Tegsedi (Inotersen): An Antisense Oligonucleotide Approved for the Treatment of Adult Members with Hereditary Transthyretin Amyloidosis. *Pharmaceuticals*, *12*(2), 78. Doi:10.3390/ph12020078
10. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Institute for Clinical and Economic Review. August 29, 2018
11. Amyloidosis Research Consortium. 2022. FDA approves AMVUTTRA for treatment of hATTR amyloidosis with polyneuropathy - Amyloidosis Research Consortium. [online] Available at: https://arci.org/fda-approves-amvuttra/ [Accessed 9 August 2022].
12. Clinicaltrials.gov. 2022. HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) - Full Text View - ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT03759379 [Accessed 9 August 2022].

SUMMARY OF REVIEW/REVISIONS	DATE
New Criteria	Q3 2022