



ATTR (transthyretin amyloid) Amyloidosis Medical Drug Criteria with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date
5/1/2023

Date of Origin

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Amvuttra™ (vutrisiran) Subcutaneous injection	The treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		10
Onpattro® (patisiran) Intravenous infusion	The treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		9
Tegsedi® (inotersen) Subcutaneous injection	The treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		1
Vyndamax™ (tafamidis) Capsule	For the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization		2
Vyndaqel® (tafamidis) Capsule	For the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization		2

See package insert for FDA prescribing information: <https://dailymed.nlm.nih.gov/dailymed/index.cfm>

CLINICAL RATIONALE

Amyloidosis	Amyloidosis is a protein disorder in which proteins misfold, then clump together to form amyloid fibrils which deposit into organs.(3) Transthyretin (TTR) is a protein primarily synthesized in the liver and carries thyroxine and retinol-binding protein. Dissociation of TTR followed by aggregation and misfolding of the TTR protein
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	<p>causes formation of insoluble amyloid fibrils. These fibrils deposit systemically, causing neuropathy and other systemic malfunctions, particularly cardiomyopathy.(4) There are two types of ATTR amyloidosis: hereditary ATTR (hATTR or ATTRm) and wild-type ATTR (ATTRwt). Hereditary ATTR results from an inherited change in the DNA that encodes for an unstable TTR protein, making TTR more likely to form amyloid fibrils. Wild-type ATTR is a result of aging; as one gets older, normal TTR protein becomes unstable, misfolding and forming amyloid fibrils.(3)</p>
Neuropathy	<p>A range of sensory and motor impairments are reported by patients with hATTR amyloidosis with polyneuropathy. The most common of these include neuropathic pain, altered sensation (i.e. decreased pain sensation), numbness, and tingling, along with muscle weakness and impaired balance which lead to difficulty walking. The pathologic process typically involves small-fiber damage early in the disease course, often with subsequent damage to peripheral motor and sensory nerves that results in sensorimotor polyneuropathy. Autonomic impairment is also frequently observed, and includes nausea and vomiting, changes in gastrointestinal motility, orthostatic hypotension, bladder dysfunction, and erectile dysfunction. Historically, measuring the disease has utilized the Familial Amyloidotic Polyneuropathy (FAP) staging system and/or the polyneuropathy disability (PND) scoring system. Recently developed and used in hATTR amyloidosis studies is the modified Neuropathy Impairment Score +7 (NIS+7). This system is more sensitive to disease progression over shorter time periods and better at capturing the different features of polyneuropathy.(5)</p> <p>Diagnosis of hATTR neuropathy can be challenging without positive family history as clinical presentation may mimic various peripheral neuropathies. In patients with peripheral neuropathy of otherwise undetermined etiology, early search for associated clinical features, especially cardiac involvement can help reveal amyloidosis. Diagnosis can be confirmed by biopsy or genetic testing.(7)</p>
Cardiomyopathy	<p>Cardiomyopathy is a manifestation of ATTR amyloidosis in which transthyretin protein misfolds to form fibrils that deposit in the heart, leading to cardiomyopathy and symptoms of heart failure. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a late-onset disease; symptoms are predominately manifested in male patients 60 years of age or older. The condition can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene TTR (ATTRm) or by the deposition of wild-type transthyretin protein (ATTRwt). There are more than 120 pathogenic mutations in TTR that result in a variable phenotypic presentation. The prevalence of ATTRwt is uncertain, some studies have reported a prevalence of 13% among patients with heart failure with a preserved ejection fraction, 16% among patients undergoing transcatheter aortic-valve replacement for severe aortic stenosis, and 5% among patients with presumed hypertrophic cardiomyopathy. Treatments have previously been limited to supportive care. Median survival in untreated patients is reported to be 2.5 years after diagnosis for ATTRm caused by the TTR Val122Ile mutation and 3.6 years for ATTRwt. Patients with ATTR-CM often show common signs and symptoms of heart failure, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, fatigue, exercise intolerance, dizziness/syncope, palpitations, electrical conduction abnormalities, and arrhythmias. Therefore, ATTR-CM is sometimes mistakenly diagnosed as hypertrophic cardiomyopathy or as generic, undifferentiated heart failure with preserved ejection fraction rather than as amyloidosis.(6,8)</p> <p>Patients with suspected ATTR-CM should include testing for monoclonal protein followed by scintigraphy or biopsy. Nuclear imaging can also be performed for additive information. In some cases, endomyocardial biopsy is necessary for a definitive diagnosis but if no monoclonal protein is detected and a diagnosis of light chain amyloidosis (AL) has been ruled out, scintigraphy alone can definitively diagnose ATTR-CM. If ATTR-CM is identified, TTR genotyping should be performed.(8)</p>
Efficacy	<p>Inotersen is an antisense oligonucleotide 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 NEURO-TTR trial randomized 172 hereditary transthyretin amyloidosis with polyneuropathy patients in a 2:1 ratio to receive 300mg of inotersen (112) or placebo (60). Primary endpoints were the change in the mNIS+7 score and the change in the Norfolk QOL-DN score. At 66 weeks, both primary efficacy assessments favored inotersen. The least squares mean</p>

change from baseline was -19.7 points (95% CI, -26.4 to -13.0; p less than 0.001) for the mNIS and -11.7 points (95% CI, -18.3 to -5.1; P less than 0.001) for the Norfolk QOL-DN score. Improvements were independent of disease stage, mutation type, or presence of cardiomyopathy.(1)

Tafamidis is a selective stabilizer of transthyretin. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process. Efficacy was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM. Patients were randomized in a 1:2:2 ration to receive Vyndaquel 20 mg, Vyndaquel 80 mg, or placebo once daily for 30 months, in addition to standard of care (e.g. diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). The primary analysis points were all-cause mortality and frequency of cardiovascular-related hospitalizations. The analysis demonstrated a significant reduction in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled Vyndaquel group.(2)

Patisiran is a double-stranded small interfering ribonucleic acid (siRNA). Patisiran causes the degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The APOLLO trial randomized 225 patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive IV patisiran (0.3 mg/kg) (148 patients) or placebo (77 patients) once every 3 weeks. The primary endpoint was the change in baseline on the modified Neuropathy Impairment Score+7 (mNIS+7), while other assessments were the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, 10-meter walk test, and modified body-mass index times albumin level as a marker of nutritional status.(9)

At 18 months, the least squares mean change for mNIS+7 was -6.0 ± 1.7 in the treatment group versus 28.0 ± 2.6 in the placebo group (-34.0 points, p less than 0.001). The change in Norfolk QOL-DN was -6.7 ± 1.8 versus 14.4 ± 2.7 (-21.1 points, p less than 0.001). Gait speed in the 10-meter walk test was increased (0.08 ± 0.02 m/s vs -0.24 ± 0.04 m/s, difference 0.31 m/s, $p < 0.001$), as was a decrease in the lowering of the BMI (-3.7 ± 9.6 versus -119.4 ± 14.5 , 115.7 difference, p less than 0.001). Patisiran has been shown to stabilize or improve a patient's PND and FAP scores through an exploratory endpoint in the APOLLO trial.(6)

Vutrisiran is a double-stranded siRNA-GalNAc (Nacetylgalactosamine) conjugate that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The efficacy of Amvuttra was evaluated in a randomized, open-label clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT03759379). Patients were randomized 3:1 to receive 25 mg of Amvuttra subcutaneously once every 3 months (N=122), or 0.3 mg/kg patisiran intravenously every 3 weeks (N=42) as a reference group. Ninety-seven percent of AMVUTTRA-treated patients and 93% of patisiran-treated patients completed at least 9 months of the assigned treatment. last max max After 25 mg every 3 months dosage in hATTR amyloidosis patients After 25 mg single dose in healthy subjects Based on population PK model estimation Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 mcg/mL to 19% at 50 mcg/mL) After single subcutaneous vutrisiran dose from 5 to 300 mg (i.e.,

	<p>0.2 to 12 times the recommended dose) in healthy subjects 2 Efficacy assessments were based on a comparison of the AMVUTTRA arm of Study 1 with an external placebo group in another study (NCT01960348) composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis.(8)</p> <p>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. The clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The Norfolk QoL-DN has a total score range from -4 to 136, with higher scores representing greater impairment. Additional endpoints were gait speed, as measured by the 10-meter walk test (10MWT), and modified body mass index (mBMI). Treatment with Amvuttra in Study 1 resulted in statistically significant improvements in the mNIS+7, Norfolk QoL-DN total score, and 10-meter walk test at Month 9 compared to placebo in the external study ($p < 0.001$) [Table 3, Figure 1, and Figure 3]. The distributions of changes in mNIS+7 and Norfolk QoL-DN total scores from baseline to Month 9 by percent of patients are shown in Figure 2 and Figure 4, respectively. The change from baseline to Month 9 in modified body mass index nominally favored Amvuttra.(8)</p>
Safety	<p>Tegsedi has a boxed warning for thrombocytopenia. Tegsedi causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. Testing prior to treatment and monitoring during treatment is required. Tegsedi also has a black box warning for glomerulonephritis. Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. Testing prior to treatment and monitoring during treatment is required. Tegsedi is available only through a restricted distribution program.(1)</p> <p>Tegsedi has the following contraindications:(1)</p> <ul style="list-style-type: none"> • Platelet count below $100 \times 10^9/L$ • History of acute glomerulonephritis caused by inotersen • Patients with a hypersensitivity reaction to inotersen <p>Amvuttra, Onpattro, Vyndaqel and Vyndamax have no boxed warnings or contraindications.(2,9,10)</p>

REFERENCES

Number	Reference
1	Tegsedi prescribing Information. Akcea Pharmaceuticals. June 2022.
2	Vyndaqel and Vyndamax prescribing information. Pfizer, Inc. June 2021.
3	Cleveland Clinic. Amyloidosis: ATTR. https://my.clevelandclinic.org/health/diseases/17855-amyloidosis-attr .
4	Kapoor M, Rossor AL, Laura M, et. al. Clinical Presentation, Diagnosis and Treatment of TTR Amyloidosis. Journal of Neuromuscular Diseases. 6 (2019) 189-

Number	Reference
	199. https://content.iospress.com/download/journal-of-neuromuscular-diseases/jnd180371?id=journal-of-neuromuscular-diseases%2Fjnd180371
5	Dyck PJ, Gonzalez-Duarte A, Obici L, et. al. Development of Measures of Polyneuropathy Impairment in hATTR Amyloidosis: From NIS to mNIS+7. Journal of the Neurological Sciences. Volume 405, 15 October 2019. https://www.sciencedirect.com/science/article/pii/S0022510X19303569
6	Maurer MS, Schwartz JH, Gundapeneni BG, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. <i>NEJM</i> 2018; 379: 1007-16. https://www.nejm.org/doi/full/10.1056/NEJMoa1805689
7	Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care. <i>Ther Clin Risk Manag.</i> 2020;16:109-123. doi:10.2147/TCRM.S219979.
8	Maurer, Mathew S et al. "Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis." <i>Circulation. Heart failure</i> 2019;12(9):e006075. doi:10.1161/CIRCHEARTFAILURE.119.006075.
9	Onpattro prescribing information. Alnylam Pharmaceuticals, Inc. July 2022.
10	Amvuttra prescribing information. Alnylam Pharmaceuticals, Inc. June 2022.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
Tegsedi	inotersen sod subcutaneous pref syr	284 MG/1.5ML	M ; N ; O ; Y	N		
Onpattro	patisiran sodium iv soln	10 MG/5ML	M ; N ; O ; Y	N		
Vyndamax	tafamidis cap	61 MG	M ; N ; O ; Y	N		
Vyndaqel	tafamidis meglumine (cardiac) cap	20 MG	M ; N ; O ; Y	N		
Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5ML	M ; N ; O ; Y	N		07-25-2022

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5 ML	1	SYRNG	90	DAYS				07-25-2022
Onpattro	Patisiran Sodium IV Soln 10 MG/5ML (2 MG/ML) (Base Equiv)	10 MG/5ML	15	MLS	21	DAYS				
Tegsedi	Inotersen Sod Subcutaneous Pref Syr 284 MG/1.5ML (Base Eq)	284 MG/1.5 ML	4	SYRNGS	28	DAYS				
Vyndamax	Tafamidis Cap 61 MG	61 MG	30	CAPS	30	DAYS				
Vyndaqel	Tafamidis Meglumine (Cardiac) Cap 20 MG	20 MG	120	CAPS	30	DAYS				

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5ML	Commercial ; HIM ; ResultsRx
Onpattro	patisiran sodium iv soln	10 MG/5ML	Commercial ; HIM ; ResultsRx
Tegsedi	inotersen sod subcutaneous pref syr	284 MG/1.5ML	Commercial ; HIM ; ResultsRx
Vyndamax	tafamidis cap	61 MG	Commercial ; HIM ; ResultsRx
Vyndaqel	tafamidis meglumine (cardiac) cap	20 MG	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5ML	Commercial ; HIM ; ResultsRx
Onpattro	Patisiran Sodium IV Soln 10 MG/5ML (2 MG/ML) (Base Equiv)	10 MG/5ML	Commercial ; HIM ; ResultsRx

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Tegsedi	Inotersen Sod Subcutaneous Pref Syr 284 MG/1.5ML (Base Eq)	284 MG/1.5ML	Commercial ; HIM ; ResultsRx
Vyndamax	Tafamidis Cap 61 MG	61 MG	Commercial ; HIM ; ResultsRx
Vyndaqel	Tafamidis Meglumine (Cardiac) Cap 20 MG	20 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	<p>Initial Evaluation</p> <p>Target Agent(s) will be approved when ALL of the following are met:</p> <ol style="list-style-type: none"> 1. The patient has ONE of the following: <ol style="list-style-type: none"> 1. ALL of the following: <ol style="list-style-type: none"> 1. A diagnosis of polyneuropathy of hereditary transthyretin-mediated amyloidosis confirmed by testing (e.g., genetic testing, biopsy) AND 2. The requested agent is FDA approved for use in polyneuropathy of hereditary transthyretin-mediated amyloidosis AND 3. The patient has clinical manifestations of polyneuropathy (e.g., neuropathic pain, altered sensation, numbness, tingling, impaired balance, motor disability) OR 2. ALL of the following: <ol style="list-style-type: none"> 1. A diagnosis of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis confirmed by testing [e.g., stannous pyrophosphate (PYP) scanning, monoclonal antibody studies, biopsy, scintigraphy, genetic testing (TTR genotyping)] AND 2. The requested agent is FDA approved for use in cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis AND 3. The patient has clinical manifestations of cardiomyopathy (e.g., dyspnea, fatigue, orthostatic hypotension, syncope, peripheral edema) OR 3. The patient has another FDA approved indication for the requested agent and route of administration AND 2. ONE of the following: <ol style="list-style-type: none"> 1. The patient's age is within FDA labeling for the requested indication for the requested agent OR 2. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication AND 3. The patient has NOT received a liver transplant AND 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND 5. The patient will NOT be using the requested agent in combination with another agent targeted in this program for the requested indication AND 6. The patient does NOT have any FDA labeled contraindications to the requested agent <p>Length of Approval: 12 months</p> <p>NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria section below.</p> <p>Renewal Evaluation</p>

Module	Clinical Criteria for Approval
	<p>Target Agent(s) will be approved when ALL of the following are met:</p> <ol style="list-style-type: none"> 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process AND 2. The patient has had clinical benefit with the requested agent AND 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND 4. The patient has NOT received a liver transplant AND 5. The patient will NOT be using the requested agent in combination with another agent targeted in this program for the requested indication AND 6. The patient does NOT have any FDA labeled contraindications to the requested agent <p>Length of Approval: 12 months</p> <p>NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria section below.</p>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	<p>Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met:</p> <ol style="list-style-type: none"> 1. The requested quantity (dose) does NOT exceed the program quantity limit OR 2. ALL of the following: <ol style="list-style-type: none"> A. The requested quantity (dose) is greater than the program quantity limit AND B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication AND C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit <p>Length of Approval: 12 months</p>