ATTR (transthyretin amyloid) Amyloidosis Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
04-01-2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Amvuttra® (vutrisiran) Subcutaneous injection	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		10
Onpattro® (patisiran) Intravenous infusion	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		9
Tegsedi® (inotersen) Subcutaneous injection	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
WAINUA™ (eplontersen) Subcutaneous injection	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		11

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 bind 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 causes formation of insoluble amyloid fibrils. These fibrils deposit systemically, causing multisystem disease with rapidly progressing polyneuropathy and other systemic manifestations, particularly cardiomyopathy.(4,5) There are two types of ATTR (transthyretin amyloid) amyloidosis: hereditary ATTR (hATTR or ATTRm) and wild-type ATTR (ATTRwt). Hereditary ATTR results from an inherited mutation 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 and sex; as one gets older, normal TTR protein becomes unstable, misfolding and forming amyloid fibrils.(3)
Neuropathy	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. However, these scales provide only a generic indicator of overall disease status and are not sensitive to track disease progression in the short-term period. Recently developed and used in hATTR amyloidosis studies is the modified Neuropathy Impairment Score +7 (NIS+7). This system is highly standardized, quantitative, and referenced assessments to quantify decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment. NIS+7 is more sensitive to disease progression over shorter time periods and better at capturing the different features of polyneuropathy. This scale has been further modified (mNIS+7 Alnylam and mNIS+7 Ionis) to afford more sensitive detection of disease progression.(5,7) 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 demonstration of amyloid in a biopsy sample and/or detection of any amyloidogic mutation by TTR genetic testing.(7)
Cardiomyopathy	Cardiomyopathy is a manifestation of ATTR amyloidosis in which transthyretin protein misfolds to form fibrils that deposit in the myocardium, 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.(6) 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)

	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)
Efficacy	Inotersen is an antisense oligonucleotide (ASO) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The efficacy of Tegsedi was demonstrated in the NEURO-TTR trial, a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy cause by hATTR amyloidsis (Study 1; NCT 01737398) Patients were randomized in a 2:1 ratio to receive either Tegsedi (113 patients) or placebo (60 patients), as a subcutaneous injection once per week for 65 weeks. Seventy seven percent of Tegsedi-treated patients and 87% of patients on placebo completed 66 weeks. Patients were FAP stage 1 or 2 (ambulatory or ambulatory with assistance, respectively) and had no prior liver transplant or anticipated liver transplant within 1 year of screening. 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 change from baseline was -19.7 points (95% CI, -26.4 to -13.0; p<0.001) for the mNIS+7 and -11.7 points (95% CI, -18.3 to -5.1; P<0.001) for the Norfolk QOL-DN score.(1) Tafamidis is a selective stabilizer of TTR. 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-cardiomyopathy (ATTR-CM), with no prior liver or heart transplantation. Patients were randomized in a 1:2:2 ratio to receive Vyndaqel 20 mg (88 patients), Vyndaqel 80 mg (176 patients), or placebo (177 patients) 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 Vyndaqel group.(2) Vutrisiran is a double-stranded small interfering ribonucleic acid (siRNA) that targets mutant and wild-type transthyretin (TTR) messenger RNA (mRNA) and covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes. This double-stranded siRNA-GalNAc conjugate 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. Of the 122 patients receiving Amvuttra, 118 received at least 18 months of treatment. 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.(10) 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). The change from baseline to Month 9 in modified body mass index nominally favored Amvuttra. Patients receiving.(10) 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 efficacy of Onpattro was demonstrated in the APOLLO trial (NCT 01960348), a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis. Patients were randomized in a 2:1 ratio, to receive IV patisiran (0.3 mg/kg) (148 patients) or placebo (77 patients) once every 3 weeks for 18 months. Patients had a Neuropathy Impairment Score (NIS) of 5-130 and no prior liver transplant or plans to undergo liver transplant during the study period. The primary endpoint was the change in baseline to Month 18 in 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, difference -34.0 points (p<0.001). The change in Norfolk QOL-DN was -6.7 (+/- 1.8) versus 14.4 (+/- 2.7), difference -21.1 points (p<0.001). Gait speed in the 10-meter walk test (m/s) was increased 0.08 (+/-0.02) versus -0.24 (+/- 0.04), 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), difference 115.7 (p<0.001).(9) Eplontersen is a transthyretin-directed ASO 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 efficacy of WAINUA was demonstrated in a randomized, open-label, multicenter trial and adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT04136184). Patients were randomized in a 6:1 ration to receive subcutaneous injections of either 45mg of WAINUA once every 4 weeks (144 patients), or 284mg of inotersen once weekly (24 patients), respectively. Efficacy assessments were based on a comparison of the WAINUA arm of Study 1 with an external placebo group (60 patients) from another study (NCT01737398) of a comparable population of adult patients with the same indication. Endpoint was change from baseline to week 35 in the mNIS+7 composite score and change from baseline to week 35 in the QoL-DN total score. Treatment with WAINUA resulted in statistically significant improvements in the mNIS+7 and Norfolk QoL-DH total scores compared to placebo control (p<0.001) at week 35. The least squares mean change from baseline was -9.0 points (95% CI, -13.5 to -4.5; p<0.001) for the mNIS+7 and -11.8 points (95% CI, -16.5 to -6.8; P<0.001) for the Norfolk QoL-DN score.(11)
Safety	Tegsedi has a the following boxed warnings:(1) • Thrombocytopenia: Tegsedi causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. Tegsedi is contraindicated in patients with a platelet count below 100 x 10^9/L. Prior to starting Tegsedi, obtain a platelet count. During treatment,

	monitor platelet counts weekly if values are 75 x 10^9/L or greater, and more frequently if values are less than 75 x10^9/L. • Glomerulonephritis: Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. Tegsedi should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher. Prior to starting Tegsedi, measure serum creatinine, estimated glomerular filtration rate (eGFR), UPCR, and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every two weeks. Tegsedi should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause. If a dose is held, once eGFR increases to greater than or equal to 45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, Tegsedi should be permanently discontinued. • Tegsedi REMS Program: Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, Tegsedi is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS). Tegsedi has the following contraindications:(1) • Platelet count below 100 x10^9/L • History of acute glomerulonephritis caused by inotersen • History of a hypersensitivity reaction to inotersen Amvuttra, Onpattro, Vyndaqel, Vyndamax and Wainua have no boxed warnings or contraindications.(2,9,10,11)

REFERENCES

Number	Reference
1	Tegsedi prescribing Information. Akcea Pharmaceuticals, Inc. June 2022.
2	Vyndaqel and Vyndamax prescribing information. Pfizer, Inc. April 2023.
3	Cleveland Clinic. Amyloidosis: ATTR. https://my.clevelandclinic.org/health/diseases/17855-amyloidosis-attr.
4	Kapoor M, Rossor AM, Laura M, et al. Clinical Presentation, Diagnosis and Treatment of TTR Amyloidosis. Journal of Neuromuscular Diseases. 6 (2019) 189-199. 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 B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 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. Ther Clin Risk Manag. 2020;16:109-123. doi:10.2147/TCRM.S219979.
8	Maurer MS, Bokhari S, Damy T, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. *Circ Heart Fail.* 2019;12(9):e006075. doi:10.1161/CIRCHEARTFAILURE.119.006075.
9	Onpattro prescribing information. Alnylam Pharmaceuticals, Inc. January 2023.

Number	Reference
10	Amvuttra prescribing information. Alnylam Pharmaceuticals, Inc. February 2023.
11	WAINUA prescribing information. AstraZeneca Pharmaceuticals LP. December 2023.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J0225	Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5ML	M ; N ; O ; Y	N		
J0222	Onpattro	patisiran sodium iv soln	10 MG/5ML	M ; N ; O ; Y	N		
	Tegsedi	inotersen sod subcutaneous pref syr	284 MG/1.5ML	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		
	Wainua	eplontersen sodium subcutaneous soln auto-inj	45 MG/0.8ML	M ; N ; O ; Y	N		

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
Amvuttra	vutrisiran sodium soln prefilled syringe	25 MG/0.5 ML	1	Syringe	90	DAYS			
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	Syringes	28	DAYS			
Vyndamax	Tafamidis Cap 61 MG	61 MG	30	Capsules	30	DAYS			
Vyndaqel	Tafamidis Meglumine (Cardiac) Cap 20 MG	20 MG	120	Capsules	30	DAYS			
Wainua	eplontersen sodium subcutaneous soln auto-inj	45 MG/0.8 ML	1	Pen	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

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Vyndamax	tafamidis cap	61 MG	Commercial ; HIM ; ResultsRx
Vyndaqel	tafamidis meglumine (cardiac) cap	20 MG	Commercial ; HIM ; ResultsRx
Wainua	eplontersen sodium subcutaneous soln auto-inj	45 MG/0.8ML	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
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
Wainua	eplontersen sodium subcutaneous soln auto-inj	45 MG/0.8ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has ONE of the following: A. ALL of the following: 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** B. ALL of the following: 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** C. The patient has another FDA approved indication for the requested agent and route of administration **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. 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**

Module	Clinical Criteria for Approval
	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 **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria section below. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 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 **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria section below.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds 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 **Length of Approval:** 12 months