Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH025.1024	**MISCELLANEOUS PRODUCTS** **TRANSTHYRETIN (TTR) LOWERING AGENTS** See Appendix A for medications covered by policy
Effective Date: 1/1/2025	**Review/Revised Date**: 12/18, 08/19, 08/20, 08/21. 08/22, 10/22, 09/23, 05/24, 09/24 (TVNT)
Original Effective Date: 04/19	**P&T Committee Meeting Date**: 02/19, 10/19, 10/20, 10/21, 12/22, 10/23, 06/24, 10/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B: Amvuttra® and Onpattro® Only
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:

1. Diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy

AND

2. Documentation of a pathogenic TTR mutation

AND

3. Patient has a baseline polyneuropathy disability (PND) score of less than or equal to IIIB **OR** has a baseline familial amyloid polyneuropathy (FAP) stage of I or II

AND

4. Baseline neuropathy impairment score (NIS) between 5 and 130

AND

5. Demonstrate symptoms consistent with polyneuropathy of hATTR amyloidosis including **at least two** symptoms of peripheral sensorimotor polyneuropathy and/or autonomic neuropathy listed below:
    a. Peripheral sensorimotor polyneuropathy: tingling or increased pain in the hands, feet, hands and/or arms, loss of feeling in the hands and/or feet,

numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking

b. Autonomic neuropathy: orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomia (constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety)

AND

6. For Tegsedi: Documentation of platelet count greater than 100 x 10^9/L

AND

7. Dose and frequency are in accordance with FDA-approved labeling

Reauthorization:

1. Documentation that patient is tolerating applicable therapy

AND

2. Documented improvement or stabilization in polyneuropathy symptoms from baseline, defined as improvement or stabilization from baseline in the Neuropathy impairment score (NIS) **AND** at least one of the following measures:
    a. Baseline polyneuropathy disability (PND) score
    b. Familial amyloid polyneuropathy (FAP) stage

EXCLUSION CRITERIA:

- New York Heart Association (NYHA) Heart Functional class III or IV
- History of liver transplantation
- Peripheral neuropathy attributed to causes other than hATTR
- Used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [such as Amvuttra® (vutrisiran), inotersen (Tegsedi®), patisiran (Onpattro®), eplontersen (Wainua®) or tafamidis (Vyndaqel®, Vyndamax®)]

AGE RESTRICTIONS:

Approved for patients 18 years of age and older

PRESCRIBER RESTRICTIONS:

Prescribed by or in consultation with a neurologist, cardiologist, or a physician who specializes in the treatment of amyloidosis

COVERAGE DURATION:

Initial authorization will be approved for six months. Reauthorization will be approved for 12 months.

QUANTITY LIMIT:

Amvuttra® (vutrisiran): four syringes per year

Tegsedi® (inotersen): four syringes per 28 days
Wainua® (eplontersen): one syringe (45mg/0.8 mL) per 30 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Hereditary ATTR (hATTR) amyloidosis with polyneuropathy is a progressive, life-threatening disease that is caused by misfolded transthyretin (TTR) protein. There have been over 120 TTR mutations that have been reported. The V30M mutation is strongly associated with polyneuropathy and is the most prevalent cause of FAP worldwide[19]. The misfolded protein accumulates as amyloid fibrils in various organs including the nerves, heart, and gastrointestinal tract. Patients experience a range of life-impacting symptoms including burning neuropathic pain, loss of sensation in hands and feet, diarrhea/constipation, sexual impotence, and dizziness/fainting.

Patisiran (Onpattro®), Inotersen (Tegsedi®), vutrisiran (Amvuttra®), and eplontersen (Wainua™) are novel, orphan designated gene therapies approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Patisiran is a double-stranded small interfering RNA (siRNA) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Patisiran is administered intravenously once every three weeks.

Inotersen is an antisense oligonucleotide that causes degradation of mutant and wild-type TTR messenger RNA (mRNA) through binding to the transthyretin (TTR) mRNA. Inotersen is administered subcutaneously once weekly.

Vutrisiran is a double-stranded small interfering RNA (siRNA) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Vutrisiran is administered subcutaneously once every three months.

Eplontersen is an antisense oligonucleotide-Ga1NAc conjugate 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.

FDA APPROVED INDICATION:

- Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

POSITION STATEMENT:

Patisiran and inotersen are the first FDA approved treatments for hATTR associated polyneuropathy. Vutrisiran and eplontersen were subsequently approved by the FDA for hATTR associated polyneuropathy.

Disease Severity Measurement Tools for patisiran, inotersen, vutrisiran, and eplontersen:

- **Familial Amyloid Polyneuropathy (FAP)** – FAP stage I- unimpaired ambulation, FAP stage II- requirement for assistance with ambulation, FAP stage III- wheelchair confinement
- **Neuropathy impairment score (NIS)** – This score is out of a total of 244 points, with higher scores indicating worse impairment. It is a clinical exam-based neuropathy evaluation that assesses motor strength/weakness (NIS-W) and reflexes (NIS-R)]. [weakness (NIS-W) and reflexes (NIS-R)]. The range of 5-130 was selected for study inclusion criteria to include patients with disease sufficiently advanced to show progression in the placebo group, but not so advanced as to preclude detection of a change in disease status.
- **Modified Neuropathy Impairment Score+7 (mNIS+7)** – Comprised of the NIS and the +7. The NIS is a clinical exam-based neuropathy evaluation [assessing both weakness (NIS-W) and reflexes (NIS-R)]; the +7 is an objective evaluation of small and large nerve fiber function [including NCS and quantitative sensory testing (QST)], as well as measurements of autonomic function (postural blood pressure). Higher scores indicate more severe neuropathy. The author's basis for using this modified score is because NIS does not adequately address sensory loss over the body and does not include nerve conduction scores.

  - Of note, the mNIS+7 scale used in the trial for patisiran is slightly different than the mNIS+7 scale used in the inotersen clinical trial.
  - At this time, a clinically meaningful decrease in the mNIS+7 score has not been established.
- **Polyneuropathy disability (PND) score** – This is how the disease is staged. Stage 0- no impairment, stage I- sensory disturbances, but preserved walking capability, stage II- impaired walking capability, but ability to walk without a stick or crutches, stage IIIA- walking only with the help one stick or crutch, stage IIIB- walking with the help of two sticks or crutches, and stage IV- confined to a wheelchair or bedridden. All patients in the clinical trial had a PND score ≤IIIb.
- **Norfolk-Quality of Life-Diabetic Neuropathy (Norfolk-QoL-DN)** – A 47-item questionnaire that assesses neuropathy symptoms and physical functioning, activities of daily living (ADL), symptoms of small and large fiber neuropathy, and autonomic neuropathy. Scores can range from -4 to 136, with higher scores indicating more impairment. This also evaluates small and large nerve fibers function in addition to automatic impairment and activities of daily living.

Clinical Summary for patisiran (Onpattro®):
The efficacy and safety of patisiran for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis was evaluated in a randomized, double-blind, global, phase III trial (APPOLO) consisting of 225 patients.

- Key inclusion criteria included: adults 18-85 years old, a documented pathogenic variant in TTR gene diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, NIS of 5 to 130, and a polyneuropathy disability (PND) score ≤IIIb.
- Key exclusion criteria included: New York Heart Association (NYHA) class III or IV, acute coronary syndrome within past 3 months, taking in combination with another transthyretin lowering agents (tafamidis, patisiran, or inotersen), uncontrolled cardiac arrhythmia or unstable angina, prior liver transplant, known type I or type II diabetes for ≥ 5 years, previous organ transplants requiring immunosuppression, and malignancy within the past 5 years.

Patients were randomized to receive either patisiran (0.3 mg/kg) or placebo intravenously once every three weeks with randomization stratified by NIS score, presence of the V30M mutation, and previous use of a transthyretin stabilizer.
The primary end point was the change from baseline to 18 months in the modified neuropathy impairment +7 score (mNIS+7). Selected secondary endpoints included a quality-of-life assessment (Norfolk QOL-DN questionnaire), motor strength (NIS-weakness), and serum TTR protein levels.

- At 18 months, the change from baseline in the mNIS+7 was significantly lower with patisiran than with placebo. The least-squares mean difference of -34.0

points was significant (95% confidence interval, -39.9 to -28.1; P<0.001) and no significant difference was observed in mNIS+7 scores at nine months.

- The change from baseline in the Norfolk QOL-DN questionnaire score was significantly lower in the patisiran group compared to placebo at 18 months. The least-squares mean difference was -21.1 points (95% confidence interval, -27.2 to -15.0; P<0.001) at 18 months.

Common side effects include infusion-related reactions and reduced vitamin A levels. Thus, patisiran is administered with pre-medications (dexamethasone, acetaminophen, H2 blocker and diphenhydramine) by a healthcare profession and it's recommended to monitor vitamin A levels. There are also safety concerns about the cardiovascular effects, specifically heart failure exacerbations and resulting death, with patisiran. Of note, patients with New York Heart Association Function Classification (NYHA) class III and IV heart failure were excluded from the trial. Although there isn't an FDA warning on the label, the FDA review noted in their review that these "findings are not reassuring with respect to patients with heart failure".

Clinical Summary for inotersen (Tegsedi®):

The efficacy and safety of inotersen for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis was evaluated in a randomized, double-blind, global, phase III trial (NEURO-TTR) consisting of 172 patients.

- Key inclusion criteria included: adults 18-82 years old, a documented pathogenic variant in TTR gene diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, neuropathy Impairment Score (NIS) of 10 to 130, and familial amyloid polyneuropathy (FAP) stage I or II.
- Key exclusion criteria included: New York Heart Association (NYHA) class III or IV, acute coronary syndrome within past three months, taking in combination with another transthyretin lowering agents (tafamidis, patisiran, or inotersen), uncontrolled cardiac arrhythmia or unstable angina, prior liver transplant, known type I or type II diabetes for ≥ 5 years, previous organ transplants requiring immunosuppression, and malignancy within the past 5 years.

Patients were randomized to receive either inotersen 284 mg or placebo subcutaneously once weekly with randomization stratified by FAP stage, presence of the V30M mutation, and previous use of a transthyretin stabilizer.

The primary end points were the change from baseline to 15 months in the modified neuropathy impairment +7 score (mNIS+7) and a quality-of-life assessment (Norfolk QOL-DN questionnaire) at 15 months.

- At 35 weeks, the change from baseline in the mNIS+7 was significantly lower with inotersen than with placebo. The least-squares mean difference of -8.7 points was significant (95% confidence interval, -13.5 to -3.9; P<0.001)

  - The change from baseline in the mNIS+7 was significantly lower with inotersen than with placebo at 15 months. The least-squares mean difference of -19.7 points was significant (95% confidence interval, -26.4 to -13.0; P<0.001).
- At 35 weeks, the change from baseline in the Norfolk QOL-DN was significantly lower with inotersen than with placebo at 35 weeks. The least-squares mean difference of -6.1 points was significant (95% confidence interval, -11.8 to -0.5; P=0.03).
  - At 15 months, the change from baseline in the Norfolk QOL-DN was significantly lower with inotersen than with placebo at 15 months. The least-squares mean difference of -11.7 points was significant (95% confidence interval, -18.3 to -5.1; P<0.001)

Inotersen does carry black-box warning for thrombocytopenia and glomerulonephritis. Thus, a REMS program requires prescribers to be certified and complete training, and patients must enroll and comply with ongoing monitoring parameters (specifically, CBC weekly and renal function bi-weekly). However, there is evidence to support that these severe events may represent a drug-disease interaction based on integrated analysis of clinical data with antisense oligonucleotides from the same 2'-O-methoxy-ethyl modified chemical class.[17,18] Inotersen is the third antisense oligonucleotide that has been approved by the FDA.

Clinical Summary for vutrisiran (Amvuttra®):

The safety and efficacy of vutrisiran in adult patients with hATTR-PN is based on low quality evidence from a single open label, phase III trial comparing the vutrisiran arm (n= 122) with an external placebo group (n = 77) from the APOLLO study (patisiran trial).

- Key inclusion included: adults 18 to 85 years of age and diagnosis of hATTR with TTR mutation. Prior use of a TTR stabilizer was permitted (such as Vyndamax, Vyndaqel, diflunisal).
- Key exclusion included: Prior liver transplant or likely to undergo liver transplantation during the study, known other (non-hATTR) forms of amyloidosis or leptomeningeal amyloidosis, NYHA heart failure classification >2, clinically significant liver function test abnormalities, known HIV, HCV, HBV infection, received prior TTR-lowering treatment (e.g. Onpattro, Tegsedi), and has other known causes of neuropathy

  The primary endpoint was change from baseline to Month 9 in modified Neuropathy Impairment Score +7 (mNIS+7). Secondary endpoints included change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN Total Score), 10-meter walk test, and modified Body Mass Index (mBMI). Results are as follows:

Table 3: Clinical Efficacy Results (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)

Endpoint†	Baseline, Mean (SD)		Change from Baseline to Month 9, LS Mean (SEM)		AMVUTTRA-Placebo* Treatment Difference, LS Mean (95% CI)	*p*-value
	AMVUTTRA N=122 (Study 1)	Placebo* N=77 (NCT01960348)	AMVUTTRA (Study 1)	Placebo* (NCT01960348)		
mNIS+7‡	60.6 (36.0)	74.6 (37.0)	-2.2 (1.4)	14.8 (2.0)	-17.0 (-21.8, -12.2)	*p*<0.001
Norfolk QoL-DN‡	47.1 (26.3)	55.5 (24.3)	-3.3 (1.7)	12.9 (2.2)	-16.2 (-21.7, -10.8)	*p*<0.001
10-meter walk test (m/sec)§	1.01 (0.39)	0.79 (0.32)	0 (0.02)	-0.13 (0.03)	0.13 (0.07, 0.19)	*p*<0.001
mBMI¶	1058 (234)	990 (214)	7.6 (7.9)	-60.2 (10.1)	67.8 (43.0, 92.6)	*p*<0.001

CI = confidence interval; LS mean = least squares mean; mBMI = modified body mass index; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life-Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean

*External placebo group from another randomized controlled trial (NCT01960348)
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)
‡A lower number indicates less impairment/fewer symptoms
§A higher number indicates less disability/less impairment
¶mBMI: nominal p-value; body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L).

The study authors concluded that compared to external placebo, vutrisiran improved the signs and symptoms of polyneuropathy, with over 50% of patients experiencing halting or reversal of their disease.

Vutrisiran (N=122) was also compared to an in-study group using 0.3 mg/kg patisiran (N=42) for an additional secondary point, non-inferiority in serum TTR level percent reduction through Month 18. It was determined that vutrisiran was noninferior to patisiran.

For safety, the most common adverse reactions with vutrisiran (≥5%) were arthralgia, dyspnea, and decreased vitamin A. No contraindications or black box warnings were identified for this drug upon FDA approval.

Clinical Summary for eplontersen (Wainua®):
The safety and efficacy of eplontersen in adult patients with polyneuropathy caused by hATTR amyloidosis is based on low quality evidence from a randomized, open-label, multicenter clinical trial (NCT04136184) comparing eplontersen (Wainua®) once every 4 weeks (N=144) or 284 mg of inotersen (Tegsedi®) once per week (N=24) as subcutaneous injections.

- Key inclusion included: Stage 1 and Stage 2 FAP participants with the following: NIS score within protocol criteria, documented transthyretin variant by genotyping, documented amyloid deposit by biopsy

- Key exclusion included: Low Retinol level at screen, Karnofsky performance status ≤50, poor renal function, known type 1 or type 2 diabetes mellitus, other causes of sensorimotor or autonomic neuropathy (for example, autoimmune disease).

The primary endpoints were the change from baseline to Week 35 in the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score and the change from baseline to Week 35 in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. Efficacy assessments were based on a comparison of the Wainua® arm of above study with an external placebo group (N=60) in another study (NCT01737398) composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis.

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. However, results from the Tegesdi® arm were not reported, therefore, relatively efficacy is unknown.

Endpoint	Baseline, Mean (SD)		Change from Baseline to Week 35, LS Mean (SEM)		Treatment Difference LS Mean (95% CI)	p-value
	WAINUA N = 140 (Study 1)	Placebo* N = 59 (NCT01737398)	WAINUA (Study 1)	Placebo* (NCT01737398)	WAINUA - Placebo*	
mNIS+7†	79.6 (42.3)	74.1 (39.0)	0.2 (1.9)	9.2 (1.9)	-9.0 (-13.5, -4.5)	<0.001
Norfolk QOL-DN†	43.5 (26.3)	48.6 (27.0)	-3.1 (2.1)	8.7 (2.1)	-11.8 (-16.8, -6.8)	<0.001

CI = confidence interval; LS mean = least squares mean; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life-Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean.
* External placebo group from another randomized controlled trial (NCT01737398).
† Based on an analysis of covariance (ANCOVA) model. Patients with a missing mNIS+7 or Norfolk QoL-DN at Week 35 had values multiply imputed using an imputation model.

The most common adverse reactions were decreased serum vitamin A level (15%) and vomiting (9%).

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Appendix A

Medication Brand Name	Generic Name	HCPCS
Amvuttra®	vutrisiran subcutaneous injection	J0225
Onpattro®	patisiran intravenous injection	J0222
Tegsedi®	inotersen subcutaneious injection	J3490, C9399
Wainua™	eplontersen subcutaneous injection	J3490, C9399

Appendix B

Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults	
Body Weight (kilograms)	# of Vials (10mg/5mL)
<33.4	1
33.4-66.6	2
66.7-100	3
>100kg (maximum dose)	3

* Dosing for intravenously infused patisiran (Onpattro®), which may be subject to audit
** Dose rounding to the nearest vial will be required within 10% of calculated dose based on a dosing of 0.3mg/kg per dose
"Dose rounding to the nearest vial will be required within 10% of calculated dose based on a dosing of 0.3mg/kg per dose" was based on the recommendation from the Hematology/Oncology Pharmacy Association that states: "On the basis of the published data, HOPA recommends that monoclonal antibodies and other biologic agents currently available be dose rounded to the nearest vial size within 10% of the prescribed dose."