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DRUG POLICY

Familial Amyloid Polyneuropathy

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Familial Amyloid Polyneuropathy policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Onpattro (patisiran) contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Wainua (eplontersen) is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Note: Amvuttra (vutrisiran) is a transthyretin-directed small interfering RNA indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults and cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits. Refer to the Amvuttra drug policy for drug specific criteria.

This policy also informs prescribers of preferred products and provides an exception process for non-preferred products through prior authorization.

This program applies to the below products specified in this policy when used for an indication that is FDA-approved for the preferred product. Coverage for a non-preferred product is provided based on clinical circumstances that would exclude the use of the preferred product and may be based on previous use of a product. The coverage review process will ascertain situations where a clinical exception can be made. This program applies to members requesting treatment with the non-preferred product.

Table 1. Transthyretin-Directed Small Interfering RNA Products

Medication	Generic Name
Preferred Products:	
Onpattro	patisiran
Amvuttra	vutrisiran
Targeted Products:	
Wainua	eplontersen

POLICY

Must meet BOTH the Preferred Drug Plan Design and Criteria for Initial Approval when applicable.

Preferred Drug Plan Design

- A. Criteria for initial approval for Wainua (eplontersen) for polyneuropathy of hereditary transthyretin-mediated amyloidosis will only apply when one of the following criteria are met:
 1. The member has had an inadequate response to treatment, intolerable adverse event, or has a contraindication to therapy with the preferred products, Onpattro (patisiran) and Amvuttra (vutrisiran)
 2. The member is currently receiving therapy with Wainua, excluding when Wainua is obtained as samples or via manufacturer's patient assistance programs, and experiencing a positive therapeutic outcome

Required Documentation

The following information is necessary to initiate the prior authorization review:

1. Testing or analysis confirming a mutation of the TTR gene.
2. Medical records documenting baseline polyneuropathy disability (PND) score or medical records documenting baseline familial amyloid polyneuropathy (FAP) disease stage
3. Medical record documentation confirming the member demonstrates signs and symptoms of polyneuropathy and an improvement in these signs and symptoms since starting therapy for continuation

Prescriber Specialties

This medication must be prescribed by or in consultation with a neurologist, geneticist, or physician specializing in the treatment of amyloidosis.

Criteria for Initial Approval

- A. **Onpattro** may be considered **medically necessary** when ALL of the following criteria are met:

1. Member is 18 years of age or older
2. Member has a diagnosis of hereditary ATTR amyloidosis with polyneuropathy confirmed by the presence of a TTR gene mutation (e.g., V30M)
3. Member has a polyneuropathy disability (PND) score $\leq$ IIIb (see Appendix A) or member has a familial amyloid polyneuropathy (FAP) disease stage $\leq$ 2 (see Appendix C)
4. Member has clinical signs and symptoms of polyneuropathy (i.e., weakness, sensory loss, decreased motor strength, decreased gait speed)
5. Other causes of peripheral neuropathy have been assessed and ruled out (see Appendix B)
6. Member is receiving Vitamin A supplementation at the recommended daily allowance prior to initiating therapy with the requested drug and will continue to receive for duration of treatment
7. Member will not be receiving the requested medication in combination with tafamidis (Vyndaqel, Vyndamax), acoramidis (Attruby), eplontersen (Wainua) or vutrisiran (Amvuttra)

Initial approval will be for 9 months

B. Wainua may be considered **medically necessary** when ALL of the following criteria are met:

1. Member is 18 years of age or older
2. Member has a diagnosis of hereditary ATTR amyloidosis with polyneuropathy confirmed by the presence of a TTR gene mutation (e.g., V30M)
3. Member has a polyneuropathy disability (PND) score $\leq$ IIIb (see Appendix A) or member has a familial amyloid polyneuropathy (FAP) disease stage $\leq$ 2 (see Appendix C)
4. Member has clinical signs and symptoms of polyneuropathy (i.e., weakness, sensory loss, decreased motor strength, decreased gait speed)
5. Other causes of peripheral neuropathy have been assessed and ruled out (see Appendix B)
6. Member is receiving Vitamin A supplementation at the recommended daily allowance prior to initiating therapy with the requested drug and will continue to receive for duration of treatment
7. Member will not be receiving the requested medication in combination with tafamidis (Vyndamax, Vyndaqel), acoramidis (Attruby), patisiran (Onpattro), or vutrisiran (Amvuttra)

Initial approval will be for 9 months

Continuation of Therapy

Continuation of therapy may be granted for members that meet all initial criteria and have achieved a therapeutic response as evidenced by stabilization or improvement from baseline in polyneuropathy disability (PND), familial amyloid polyneuropathy (FAP) disease stage, or other assessment of disease progression and neuropathy severity (i.e., modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, neuropathy impairment score (NIS)). Documentation from the medical record must be provided.

Approval will be for 12 months

Non-Formulary Exception Criteria

Non-Formulary Exception criteria applies to formularies which do not include the requested product(s) on the formulary drug list. Meeting the criteria above may satisfy some, or all, portions of the Non-Formulary Exception Criteria. A medication that is non-formulary may be covered when the Criteria for Approval AND the following criteria are met:

1. The requested drug must be used for an FDA-approved indication, or an indication supported in the compendia of current literature (examples: AHFS, Micromedex, current accepted guidelines). Diagnostic testing/lab results required when applicable.
2. The prescribed dose/quantity must fall within the FDA-approved labeling or dosing guidelines found in the compendia of current literature.
3. All covered formulary alternative drugs on any tier will be ineffective, have been ineffective, would not be as effective as the non-formulary drug, or would have adverse effects. Documentation is required and must include chart note(s) or other documentation indicating prior treatment failure, severity of the adverse event (if any), and dosage and duration of the prior treatment, or contraindication to formulary alternatives.

Quantity/Dosing Limits Apply

Medication	Standard Limit	FDA Recommended Dosing
Onpattro (patisiran)	3 vials per 21 days	For patients weighing <100 kg: • 0.3 mg/kg every 3 weeks For patients weighing ≥100 kg: • 30 mg every 3 weeks Note: Patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines prior to infusion to prevent infusion-related reactions
Wainua (eplontersen)	1 autoinjector/syringe per 28 days	45 mg administered by subcutaneous injection once monthly

APPENDIX

A. Polyneuropathy Disability Score (PND)

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 of one stick or crutch

Stage IIIb: walking with the help of two sticks or crutches

Stage IV: confined to a wheelchair or bedridden

B. Other Causes of Peripheral Neuropathy

- a. Diabetes
- b. Glucose Intolerance
- c. Vitamin B₁₂ deficiency
- d. Charcot-Marie-Tooth disease
- e. Chemotherapeutic agents (e.g., platins, vincristine, taxanes, lenalidomide, thalidomide)
- f. Trauma
- g. Vasculitis
- h. Autoimmune diseases (e.g., Sjögren's syndrome, lupus, rheumatoid arthritis)
- i. Chronic kidney disease
- j. Vitamin B₆ toxicity
- k. Paraneoplastic syndrome
- l. Viral infections (e.g., varicella-zoster, herpes simplex, Lyme disease, West Nile, cytomegalovirus, HIV)

C. Familial Amyloid Polyneuropathy (FAP) Stages

- a. Stage 0 – Asymptomatic
- b. Stage 1 – Sensory neuropathy
- c. Stage 2 – Require assistance for walking
- d. Stage 3 – Bedridden or wheelchair bound

CLINICAL RATIONALE

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disease caused by mutations in transthyretin encoding genes. Affecting multiple organ systems, the disease is progressive and fatal, as circulating transthyretin proteins misfold, resulting in amyloid deposition to organs and tissues. Clinical manifestations include cardiomyopathies and neuropathies.

Onpattro is the first FDA-approved agent for the treatment of polyneuropathy of hATTR amyloidosis in adults. Onpattro is a small interfering RNA (siRNA), targeting transthyretin synthesis within the liver. In a phase III trial, Onpattro treatment every 3 weeks for 18 months was found to be superior to placebo in achieving a decrease from baseline in mNIS+7, demonstrating improvement in neuropathy impairment. Clinical benefit was assessed with change from baseline in Norfolk QoL-DN, favoring the Onpattro treatment group. Infusion related reactions occurred more frequently in patients receiving Onpattro. Labeling requirements include instructions for pre-medication and monitoring during infusion. Onpattro has also been found to decrease serum Vitamin A levels. Supplementation of Vitamin A during treatment is recommended. An extension study following completion of phase III trial is ongoing.

Amvuttra is the third agent to be FDA-approved for the treatment of polyneuropathy of hATTR amyloidosis in adults. Like Onpattro, Amvuttra is a small interfering RNA (siRNA) but is administered via subcutaneous (SC) injection once every 3 months by a healthcare provider. A phase III trial evaluated the safety and efficacy of Amvuttra. In this trial, Amvuttra was superior to an external placebo group at 9 months with respect to a lower rate of progression of neuropathy. Amvuttra was also superior to the external placebo group for change from baseline in quality-of-life scores. No major safety concerns were noted in the trial. Treatment with Amvuttra leads to a decrease in serum Vitamin A levels. Vitamin A supplementation at the recommended daily allowance is recommended for patients taking Amvuttra. Amvuttra is also approved for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits. Amvuttra criteria is not included in this drug policy.

Wainua is the fourth agent to be FDA-approved for the treatment of polyneuropathy of hATTR amyloidosis in adults. Like Tegsedi, Wainua is an antisense oligonucleotide targeted at hepatic synthesis of transthyretin. A phase III trial evaluated the safety and efficacy of Wainua. In this trial, Wainua was superior to an external placebo group at 35 weeks and 66 weeks with respect to lower rate of progression of neuropathy and for improvement from baseline quality of life scores. No major safety concerns were noted, but adverse events included decreased vitamin A, vomiting, proteinuria, injection site reactions, blurred vision and cataracts. Vitamin A supplementation at the recommended daily allowance is recommended for patients taking Amvuttra.

There are no formal head-to-head studies evaluating the comparative effectiveness of Onpattro, Amvuttra, and Wainua. By indirect comparison, Onpattro appears to have similar or better efficacy compared with Amvuttra, Wainua. Both Amvuttra and Onpattro require administration by a healthcare provider, while Wainua can be self-administered.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J0222 - Injection, Patisiran (Onpattro), 0.1 mg
- C9311 - Injection, Eplontersen,(Wainua) 1 mg (10/1/2026)

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- Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018; 379(1):11-21.
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- Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018; 379:22-31.
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POLICY HISTORY

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