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 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.

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

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

This policy 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
Targeted Products:	
Tegsedi	inotersen

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 Tegsedi (inotersen) for polyneuropathy of hereditary transthyretin-mediated amyloidosis will only apply when one of the following criteria are met:
    1. The patient has had an inadequate response to treatment, intolerable adverse event, or has a contraindication to therapy with the preferred product, Onpattro (patisiran)
    2. The patient is currently receiving therapy with Tegsedi, excluding when Tegsedi 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 polyneuropathy disability (PND) score and neuropathy impairment score (NIS)
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

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 is not a liver transplant recipient
    4. Member has a polyneuropathy disability (PND) score ≤ IIIb (see Appendix A)
    5. Member has clinical signs and symptoms of polyneuropathy (i.e. weakness, sensory loss, decreased motor strength, decreased gait speed)
    6. Other causes of peripheral neuropathy have been assessed and ruled out (see Appendix B)
    7. Patient 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
    8. Member will not be receiving the requested medication in combination with tafamidis (Vyndaqel, Vyndamax), inotersen (Tegsedi), or vutrisiran (Amvuttra)
    9. Medication is being prescribed by or in consultation with a neurologist or a specialist in the treatment of amyloidosis

Initial approval will be for **9 months**

B. Tegsedi 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 is not a liver transplant recipient
   4. Member has a polyneuropathy disability (PND) score ≤ IIIb
   5. Member has clinical signs and symptoms of polyneuropathy (i.e. weakness, sensory loss, decreased motor strength, decreased gait speed)
   6. Other causes of peripheral neuropathy have been assessed and ruled out (see Appendix B)
   7. Member has a baseline platelet count ≥100 x 10^9/L prior to starting therapy
   8. Member has a baseline urinary protein to creatinine ratio (UPCR) <1000mg/g prior to starting therapy
   9. Member will not be receiving the requested medication in combination with tafamidis (Vyndaqel, Vyndamax), patisiran (Onpattro), or vutrisiran Amvutrra)
   10. Medication is being prescribed by or in consultation with a neurologist or a specialist in the treatment of amyloidosis

Initial approval will be for **9 months**

C. **Amvuttra** 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 is not a liver transplant recipient
   4. Member has a polyneuropathy disability (PND) score ≤ IIIb (see Appendix A)
   5. Member has clinical signs and symptoms of polyneuropathy (i.e. weakness, sensory loss, decreased motor strength, decreased gait speed)
   6. Other causes of peripheral neuropathy have been assessed and ruled out (see Appendix B)
   7. Patient 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
   8. Member will not be receiving the requested medication in combination with tafamidis (Vyndamax, Vyndaqel), patisiran (Onpattro), or inotersen (Tegsedi)
   9. Medication is being prescribed by or in consultation with a neurologist or a specialist in the treatment of amyloidosis

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) or neuropathy impairment score (NIS).

Approval will be for **12 months**

Quantity Limits Apply

Onpattro
- 3 vials per 21 days

Tegsedi
- 4 pre-filled syringes per 28 days

Amvuttra
- 1 syringe per 3 months

Dosing

Onpattro

- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks. For patients weighing 100 kg or more, the recommended dosage is 30 mg every 3 weeks.
- Patients should receive pre-medication with a corticosteroid, acetaminophen, and antihistamines prior to infusion to prevent infusion-related reactions.

Tegsedi

- The recommended dosage is 284 mg administered by subcutaneous injection once weekly.

Amvuttra

- The recommended dosage is 25 mg administered by subcutaneous injection once every 3 months.
- Amvuttra is for subcutaneous use only and should be administered by a healthcare professional.

APPENDIX

A. Polyneuoropathy 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 B_{12} 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 B_6 toxicity
k. Paraneoplastic syndrome
l. Viral infections (e.g. varicella-zoster, herpes simplex, Lyme disease, West Nile, cytomegalovirus, HIV)

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 tranthyretin proteins misfold, resulting in amyloid deposition to organs and tissues. Clincial 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 the phase III trial is ongoing.

Tegsedi is the second agent to be FDA-approved for the treatment of polyneuropathy of hATTR amyloidosis in adults, just two months following the approval of Onpattro. Tegsedi is an oligonucleotide. Although Tegsedi and Onpattro have unique mechanisms, they both target hepatic synthesis of transthyretin. A phase III trial evaluated the safety and efficacy of Tegsedi. The primary endpoints were achieved, with significant differences from placebo in the change in the mNIS+7 and Norfolk QOL-DN scores following 15 months of treatment. Adverse events including glomerulonephritis and thrombocytopenia were reported, resulting in one death. As a result, Tegsedi will only be available through a REMS program and requires ongoing lab monitoring of platelets, serum creatinine, estimated glomerular filtration rate, and urinary protein to creatinine ratio.

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

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, 0.1 mg (effective 10/1/2019)
- J3490 Unclassified drugs
- J3590 Unclassified biologics
- C9399 Unclassified drugs or biologicals
- J0225 - Inj, vutrisiran (Amvuttra), 1mg (effective 1/1/2023)

REFERENCES

- Onpattro [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; February 2020.
- Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379:11-21.
- Tegsedi [package insert]. Boston, MA: Akcea Therapeutics, Inc. September 2020.
- Amvuttra [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; June 2022.
- Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Tranthyretin Amyloidosis. N Engl J Med. 2018;379:22-31.
- Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
- Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2021 June 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of

Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed June 14, 2022.

POLICY HISTORY

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