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Policy Number: C17894-A

Onpattro (patisiran)_Tegsedi (inotersen)

PRODUCTS AFFECTED

Onpattro (patisiran), Tegsedi (inotersen)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the me'ber's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):

1. Documented diagnosis of hereditary transthyretin-mediated amyloidosis associated polyneuropathy (hATTR-PN)
   AND
   (b) Documentation of BOTH of the following [DOCUMENTATION REQUIRED(a)

Pathogenic transthyretin (TTR) mutation verified by genetic testing

Note: More than 120 different transthyretin (TTR) gene mutations have been identified, with predominant symptom presentation varying by genotype. The most common mutations in the US are V122I, T60A, and V30M

AND

(b) ONE of the following: Polyneuropathy disability (PND) score ≤ IIIb, Familial amyloidotic polyneuropathy (FAP) stage 1 or 2, OR Neuropathy impairment score (NIS) between 10 and 130

AND

2. Documentation of presence of clinical signs and symptoms of the disease such as: Peripheral sensory-motor neuropathy (e.g., neuropathic pain, paresthesia, weakness, bilateral carpal tunnel syndrome, difficulty walking), Autonomic neuropathy (e.g., hypotension, recurrent urinary tract infections, sexual dysfunction, sweating abnormalities, urinary retention), Gastrointestinal manifestations (e.g., diarrhea, nausea, vomiting, unintentional weight loss), Cardiovascular manifestations (e.g., arrhythmias, conduction abnormalities, heart failure)
   AND
3. Documentation the member has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product (e.g., gabapentin [Neurontin], Lyrica [pregabalin capsules]) or a tricyclic antidepressant (e.g., amitriptyline, nortriptyline), or Serotonin/Norepinephrine Reuptake Inhibitors (e.g., duloxetine)
   AND
4. Prescriber attestation that member has been counseled on need for Vitamin A supplementation during therapy
   MOLINA REVIEWER: See Other Special Considerations for additional information.
   AND
5. For Onpattro (patisiran):
   a. Prescriber attests member will not receive Onpattro in combination with TTR-lowering agent, including Tegsedi OR TTR-stabilizing agent, including diflunisal, Vyndaqel, Vyndamax

   AND
6. For Tegsedi (inotersen):
   a. Documentation of ALL of the following lab results: (a) platelet count > 100 x 10^9/L, (b) renal function status (serum creatinine, urinary protein to creatinine ratio (UPCR) ≤ 1000 mg/g, urinalysis), AND (b) baseline liver function tests (ALT, AST, bilirubin). Refer to "Other Special Considerations" section.
      AND
   b. Prescriber attests member will not receive Tegsedi in combination with TTR-lowering agent, including Onpattro OR TTR-stabilizing agent, including diflunisal, Vyndaqel, Vyndamax

CONTINUATION OF THERAPY:

A. HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS ASSOCIATED POLYNEUROPATHY (hATTR-PN):
1. Documentation of a positive response to therapy (e.g., improved neurologic impairment, motor function, slowing of disease progression, cardiac parameters, improvement in baseline scores: Polyneuropathy disability (PND) score ≤ IIIb OR FAP Stage 1 or 2, neuropathy impairment score) [DOCUMENTATION REQUIRED]
   AND
2. Prescriber attests to or clinical review has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. For Tegsedi (inotersen): Prescriber attests to continued appropriate monitoring for signs or symptoms of thrombocytopenia, glomerulonephritis, other serious side effects and laboratory testing as recommended per FDA label instructions (i.e., platelet count, eGFR,

UPCR, AST, ALT, total bilirubin)

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Onpattro (patisiran): For patients weighing less than 100 kg, the recommended dosage of Onpattro is 0.3 mg/kg once every 3 weeks. For patients weighing 100 kg or more, the recommended dosage of Onpattro is 30 mg once every 3 weeks.

Tegsedi (inotersen): 284 mg/1.5mL single-dose prefilled syringe per week

Maximum Quantity Limits –
Onpattro: 3 vials every 3 weeks
Tegsedi (inotersen): 284 mg/1.5mL single-dose prefilled syringe per week

PLACE OF ADMINISTRATION:
Onpattro (patisiran): The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility- based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Onpattro (patisiran). For information on site of care, see
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

Tegsedi (inotersen): The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Onpattro (patisiran): Intravenous solution
Tegsedi (inotersen): Subcutaneous injection

DRUG CLASS:
Onpattro (patisiran): Small interfering ribonucleic acid (siRNA)
Tegsedi (inotersen): Antisense Oligonucleotide

FDA-APPROVED USES:
Indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

The polyneuropathy disability score is an additional assessment tool with ranking based on different classes I-IV. Higher scores are indicative of more impaired walking ability. The varying classes are defined as follows:
I: preserved walking, sensory disturbances
II: impaired walking without need for a stick or crutches IIIa: walking with one stick or crutch IIIb: walking with two sticks or crutches

Familial Amyloid Polyneuropathy (FAP) clinical staging:
Stage 0: no symptoms
Stage 1: unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
Stage 2: assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
Stage 3: wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all Limbs

A. Scoring Scale of Mnis+7 (the higher the score, the less function)

A) mNIS+7

Test	Component	Minimum Score	Maximum Score
NIS	Cranial Nerves	0	40
	Muscle Weakness	0	152
	Reflexes	0	20
	Sensation	0	32
Modified +7	Heart Rate Deep Breathing†	-3.72	3.72
	Nerve Conduction†	-18.6	18.6
	Touch Pressure	0	40
	Heat-Pain	0	40
mNIS+7*	**Composite**	**-22.3**	**346.3**

B. Scoring Scale of Norfolk QoL-DN (the higher the score, the poorer the quality of life)

B) Norfolk QoL-DN

Domain	Items[1,2]	Minimum Score	Maximum Score
Symptoms	Σ (1-7, 9)	0	32
Physical Functioning/Large Fiber Neuropathy	Σ (8, 11, 13-15, 24, 27-35)	-4	56
Small Fiber Neuropathy	Σ (10, 16-18)	0	16
Large Fiber Neuropathy	Σ (19-21)	0	12
Activities of Daily Living	Σ (12, 22, 23, 25, 26)	0	20
Norfolk QoL-DN*	**Total**	**-4**	**136**

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare condition affecting about 50,000people worldwide caused by a genetic mutation in the transthyretin (TTR) gene. Mutations in the TTR gene lead to de-stabilization, misfolding and aggregation into insoluble amyloid fibrils which deposit into multiple sites such as the nervous system, heart, kidneys, and eyes. There are multiple TTR mutations, the most prevalent being TTR V30M. Common symptoms of hATTR amyloidosis include peripheral sensory or autonomic neuropathy, cardiomyopathy, and GI dysfunction. As the disease progresses, symptoms can worsen and lead to life-threatening multiorgan dysfunction.

Hereditary transthyretin-mediated amyloidosis manifests as abnormal buildup of amyloids which are protein fibers that deposit in organs and tissues in consequence interfering with normal functioning. The amyloid deposits usually occur in the peripheral nervous system, which can result in a loss of sensation, pain, or immobility in the arms, legs, hands and feet. They can also deposit in heart, kidneys, eyes and gastrointestinal tract and affect their functioning. The focus of the hATTR treatment is generally symptom management.

Given the magnitude of non-specific symptoms, diagnosis of hATTR is often challenging and is commonly confused with other conditions. Treatment options include liver transplantation and a limited number of

pharmacologic therapies. While liver transplantation has been shown to eliminate the production of variant TTR protein and slow disease progression, it does not prevent cardiomyopathy as amyloids can continue to deposit in the heart. One treatment option is Vyndaqel (tafamidis), a transthyretin stabilizer, which stabilizes the tetramer of the TTR transport protein to slow the dissociation into monomers that drives TTR amyloidosis. Vyndaqel is indicated for the treatment of cardiomyopathy of wild type or hATTR amyloidosis. Recently approved treatment options for polyneuropathy of hATTR amyloidosis involve inhibition of hepatic production of TTR using a gene silencing RNA molecule, Onpattro (patisiran), and an antisense oligonucleotide, Tegsedi (inotersen).

Patisiran is a small interfering ribonucleic acid (siRNA) which works by silencing a portion of RNA involved in causing polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults. More specifically, patisiran prevents production of transthyretin (TTR) which leads to reduction in accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients better manage the condition.3 The FDA approved Onpattro in August 2018 based on data from "Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis" study. It was multicenter, international, randomized, double-blind, placebo-controlled, phase 3 trial of patisiran in patients with hATTR polyneuropathy. The primary end point was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months.
Participants were adult patients (aged 18 to 85 years) with a documented pathogenic variant in TTR; a diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, with a NIS of 5 to 130 and a polyneuropathy disability score of IIIb or lower. A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group). The mean (±SD) mNIS+7at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group; the least- squares mean (±SE) change from baseline was −6.0±1.7 versus 28.0±2.6 (difference, −34.0 points; P<0.001) at 18 months. The effect on gait speed and modified BMI was also observed at 18 months. The least- squares mean change from baseline in gait speed was 0.08±0.02 m per second with patisiran versus −0.24±0.04 m per second with placebo (difference, 0.31 m per second; P<0.001). The least-squares mean change from baseline in the modified BMI was −3.7±9.6 versus −119.4±14.5 (difference, 115.7; P<0.001). Patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis in this trial.[4]
Tegsedi (inotersen) binds to and degrades the mutant and wild-type TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The FDA approved Tegsedi in October 2018 based on data from the NEURO-TRR study, a 66-week placebo-controlled, phase 3 trial with primary
efficacy endpoints being mean change in baseline of the Modified Neuropathy Impairment Score+7 (mNIS+7) and the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score (see Appendix A and B). Participants of this study were between the ages of 18-82 years old with a diagnosis of stage 1 or 2 hATTR amyloidosis, a Neuropathy Impairment Score (NIS) between 10 – 130, a TTR mutation, and amyloid deposits confirmed through biopsy. Key exclusion criteria included NYHA Class III or higher, previous liver transplant, presence of DM associated neuropathy, and chronic kidney disease. The NEURO-TRR study showed Tegsedi to improve the course of neurologic disease in the quality of life in members with hATTR amyloidosis. Both primary endpoints showed significant benefits with Tegsedi treatment when compared to placebo.

Tegsedi REMS Program
TEGSEDI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program, because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis.
Important requirements of the TEGSEDI Prescribing Program include:
• Prescribers must be certified within the program by enrolling and completing training.
• Patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive TEGSEDI.
Further information, including a list of qualified pharmacies/distributors, is available at www.TEGSEDIREMS.com or 1-844-483-4736.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Onpattro (patisiran) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Onpattro (patisiran) include: No labeled contraindications.

Onpattro has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Coverage is not recommended for the following circumstances: Cardiomyopathy associated with hATTR amyloidosis, Primary or leptomeningeal amyloidosis, Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis or Concurrent use with Tegsedi (inotersen) injections

All other uses of Tegsedi (inotersen) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Tegsedi (inotersen) include: platelet count <100 x 10^9/L, a history of acute glomerulonephritis caused by Tegsedi, and a history of hypersensitivity reaction to Tegsedi.

OTHER SPECIAL CONSIDERATIONS:

Onpattro (patisiran):

A. Infusion-related reactions:
   a. Monitor for signs and symptoms during infusion
   b. Slow or interrupt the infusion if clinically indicated
   c. Discontinue if a serious or life-threatening infusion-related reaction occurs
B. Patisiran can lead to reduced serum vitamin A levels, vitamin A supplementation is advised if patient is taking patisiran.
   a. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur
C. Patisiran has not been studied in patients with severe renal or hepatic impairment

Tegsedi (inotersen):

Tegsedi (inotersen) has a Black Box Warning for thrombocytopenia and glomerulonephritis.

Monitoring:

Platelets: At baseline, as necessary throughout treatment and for 8 weeks (or longer if platelet counts remain <100,000/mm^3) following the discontinuation of treatment. Inotersen is contraindicated in patients with a platelet count below 100,000/mm^3

Serum creatinine, eGFR, urine protein to creatinine ratio, urinalysis: Inotersen should not be given to patients who develop a UPCR of 1,000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause

AST, ALT, total bilirubin: Monitor at baseline, every 4 months during treatment, and for 8 weeks following the discontinuation of treatment. In liver transplant patients, monitor at baseline, monthly during treatment, and for 8 weeks following the discontinuation of treatment

Onpattro and Tegsedi can lead to reduced serum vitamin A levels, vitamin A supplementation is advised if patient is taking either. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by Onpattro and Tegsedi and of vitamin A supplementation are unknown. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0222	Injection, patisiran, 0.1mg

AVAILABLE DOSAGE FORMS:
Onpattro SOLN 10MG/5ML single-dose vial
Tegsedi SOSY 284MG/1.5ML prefilled syringe

REFERENCES

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15. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Institute for Clinical and Economic Review. August 29, 2018

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information Available Dosage Forms References	Q3 2023
Q2 2022 Established tracking in new format	Historical changes on file