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Subject: Inotersen (Tegsedi™)

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DESCRIPTION:

Approximately 10,000 to 15,000 patients are diagnosed with hereditary transthyretin mediated (hATTR) amyloidosis in the United States. hATTR is a rare, progressive, and fatal multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver. Over time, these deposits cause significant neurologic problems, functional limitations, and disability. These presentations include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy [FAP]), and a predominantly cardiac phenotype (formerly known as familial cardiomyopathy), although the majority of cases express both neurologic and cardiac manifestations. hATTR profoundly impacts all aspects of quality of life. Given that the disease may affect multiple organ systems and may progress rapidly, a wide variety of manifestations may include (but are not limited to) weight loss, wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea. Some patients also develop cardiac complications, which can increase the risk of early death. The age of onset of symptoms, the types of problems patients experience, and the rate of progression vary significantly. Treatment options include liver transplant, diflunisal, patisiran (Onpattro™), and inotersen (Tegsedi™). In 2019, tafamidis meglumine (Vyndaqel®) and tafamidis (Vyndamax™) gained FDA approved for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM).

Inotersen (Tegsedi), antisense oligonucleotide 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, was approved by the U.S. Food and Drug Administration (FDA) in October 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

The efficacy of inotersen was evaluated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis. Participants were randomized to receive either inotersen 284 mg (N=113) or placebo (N=60) as a weekly subcutaneous injection for 65 weeks, with 3 doses administered during the first week of treatment. The co-primary

efficacy endpoints were the change from baseline to Week 66 in the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score and the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The changes from baseline to Week 66 on both the mNIS+7 and the Norfolk QoL-DN significantly favored inotersen as seen with an improved the modified Neuropathy Impairment Score+7 (treatment difference, -19.7 points) and the patient-reported Norfolk Quality of Life-Diabetic Neuropathy questionnaire (treatment difference, -11.7 points) at week 66 (see table 1). Significant between-group differences in both endpoints were seen at an interim analysis at week 35 (treatment differences, -8.7 and -6.1 points, respectively). Of included patients, 52% carried the Val30Met mutation (from a total of 27 mutations), 67% had stage 1 disease (ambulatory), and 63% had cardiomyopathy. In subgroup analysis, improvements in both endpoints were seen with inotersen regardless of disease stage, presence/absence Val30Met mutation, or the presence of cardiomyopathy. Inotersen was associated with a median nadir of 79% for serum transthyretin from week 13 to 65. Five deaths occurred in the inotersen group compared to none in the placebo group; 1 death was due to intracranial hemorrhage associated with thrombocytopenia. All patients received vitamin A 3000 international units daily and were randomized to either inotersen 300 mg (284 mg free acid) subQ for 3 injections the first week followed by weekly injections for 64 weeks, or placebo

Table 1: Clinical Efficacy Results from Study 1

	Baseline		Change from Baseline to Week 66 (LS Mean)		Inotersen – placebo Treatment Difference LS Mean (95% CI)	p-value
Endpoint	Inotersen	Placebo	Inotersen	Placebo		
Primarya						
mNIS+7b, c	80.2	75.3	5.8	25.5	-19.7 [-26.4, -13.0]	<0.001
Norfolk QOL-DNb, d	48.7	48.7	1.0	12.7	-11.7 [-18.3, -5.1]	<0.001

CI, confidence interval; LS, least squares; 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

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of inotersen (Tegsedi) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with hereditary ATTR (hATTR) amyloidosis with polyneuropathy or familial amyloid polyneuropathy (FAP)
2. Member has a TTR mutation – laboratory documentation must be provided
3. Member is not a liver transplant recipient

4. Member demonstrates signs and symptoms of polyneuropathy – documentation from the medical record must be provided
5. Member's polyneuropathy disability score is less than or equal to IIIb – documentation from the medical record must be provided
6. Use will not be in combination with ANY of the following:
    a. Patisiran (Onpattro)
    b. Tafamidis meglumine(Vyndaqel)
    c. Tafamidis (Vyndamax)
7. Inotersen is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 284 mg weekly (max 4 syringes/28 days)

Approval duration: 1 year

Continuation of inotersen (Tegsedi) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of hereditary ATTR (hATTR) amyloidosis or familial amyloid polyneuropathy (FAP), **OR** the member has previously met all indication-specific criteria.
2. Member has a TTR mutation – laboratory documentation must be provided
3. Member is not a liver transplant recipient
4. Member demonstrates a clinically meaningful beneficial response to treatment with inotersen compared to baseline – documentation from the medical record must be provided
5. Member's polyneuropathy disability score is less than or equal to IIIb – documentation from the medical record must be provided
6. Use will not be in combination with ANY of the following:
    a. Patisiran (Onpattro)
    b. Tafamidis meglumine (Vyndaqel)
    c. Tafamidis (Vyndamax)
7. Inotersen is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed 284 mg weekly (max 4 syringes/28 days)

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL

PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 284 mg injected subcutaneously once weekly

Dose Adjustments

- See product label

Drug Availability

- Injection: 284 mg/ 1.5 mL in a single-dose prefilled syringe

PRECAUTIONS:

Boxed Warning

- THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

Contraindications

- Platelet count less than 100 x 109/L
- History of acute glomerulonephritis
- Patients with a history of a hypersensitivity reaction

Precautions/Warnings

- Stroke and Cervicocephalic Arterial Dissection: These adverse events occurred within 2 days of first dose and with symptoms of cytokine release. Educate patients on symptoms of stroke and central nervous system arterial dissection.
- Inflammatory and Immune Effects: Serious neurologic adverse reactions consistent with inflammatory and immune effects occurred.
- Liver Effects: Monitor alanine amino transferase, aspartate aminotransferase, and total bilirubin every 4 months during treatment and in case of symptoms of hepatic dysfunction.
- Hypersensitivity Reactions: If these occur, discontinue and initiate appropriate therapy.
- Uninterpretable Platelet Counts: Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid: Platelet clumping can cause uninterpretable platelet measurement; repeat test if thesis suspected.
- Reduced Serum Vitamin A Levels and Recommended Supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3490	Unclassified drug

ICD-10 Diagnosis Codes That Support Medical Necessity

E85.1	Neuropathic heredofamilial amyloidosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Familial Amyloid Polyneuropathy (FAP) stage: Clinical staging system for the neuropathy symptoms of hATTR (formerly termed familial amyloid neuropathy).

- The scale ranges from 1 to 3, as follows:
    - FAP Stage 1: Walking without assistance, mild neuropathy (sensory, autonomic, and motor) in lower limbs
    - FAP Stage 2: Walking with assistance, moderate impairment in lower limbs, trunk, and upper limbs
    - FAP Stage 3: wheelchair or bed-ridden, severe neuropathy

Modified neuropathy impairment score +7 (mNIS+7): A composite score measuring motor strength, reflexes, sensation, nerve conduction, and autonomic function. Two versions of this composite measure were adapted from the NIS+7 to better reflect hATTR polyneuropathy and have been used as primary outcomes in inotersen and patisiran clinical trials. Neither version of the mNIS+7 has a defined threshold for clinical relevance. A 2-point change has been suggested as the minimum clinically important difference for the NIS+7; 8 however, we were unable to find literature reporting any validation specific to either version of the mNIS+7. In both scales, a lower score represents better neurologic function (e.g., an increase in score reflects worsening of neurologic impairment).

Polyneuropathy disability score (PND): A five-stage measure of neuropathy impairment ranging from 0 (no impairment) to 4 (confined to a wheelchair or bedridden).

- 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

RELATED GUIDELINES:

Patisiran (Onpattro), 09-J3000-16

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

12/15/18	New Medical Coverage Guideline.
01/15/19	Update to position statement to include comparative effectiveness language.
11/15/19	Review and revision, consisting of updating references, position statement, description
03/15/26	Retire MCG.