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Subject: Patisiran (Onpattro™)

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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).

Patisiran (Onpattro), a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, 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 August 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

The safety and efficacy of patisiran were evaluated in in a randomized, double-blind, placebo-controlled phase III trial (APOLLO) in adults with polyneuropathy caused by hATTR amyloidosis. Adult patients 18 to 85 years of age were eligible for the study if the investigatory estimated survival to be ≥ 2 years, Neuropathy Impairment Score (NIS) of 5 to 130, and polyneuropathy disability score ≤ IIIb. Patients were

randomized in to receive intravenous patisiran at a dose of 0.3 mg/kg (n = 148) or placebo (n = 77) once every 3 weeks for 18 months. All patients were premedicated with a corticosteroid, acetaminophen, and antihistamines. The primary efficacy endpoint was the change at 18 months from baseline to month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7), an objective assessment of neuropathy that measures deficits in cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The maximum possible score was 304, with higher scores associated with greater disease severity. The clinical meaningfulness of changes in the mNIS+7 was assessed by a patient-reported assessment (the Quality of Life-Diabetic Neuropathy or QoL-DN total score) that evaluates the subjective experience of neuropathy the change from baseline in terms of physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy from baseline to month 18.

Patisiran demonstrated statistically and clinically significant differences from placebo for both scores (see table 1). Overall patisiran reduced the mean max serum TTR reduction by 87.8% from baseline in the patisiran treated group over 18 months. The LS mean change in the mNIS+7 from baseline at 18 months was -33.99 (p = 9.26x10-24); (Patisiran -6.03; placebo +27.96). The LS mean change in the Norfolk QOL-DN from baseline at 18 months was -21.1 (p = 1.10x10-10); (Patisiran -6.7; placebo +14.4). All secondary endpoints (e.g., NIS-W, R-ODS, COMPASS-31, etc.) also achieved statistical significance at 18 months. The investigators also concluded that patisiran therapy was relatively safe and well tolerated with no increases in the frequency of events for patisiran compared to placebo group by system organ class. Overall, 13 deaths occurred in the APOLLO study, however, none of these were considered related to the study drugs and were consistent with natural history. The majority of infusion-related reactions were mild in severity, with no severe or life-threatening, or serious reactions.

Table 1: Clinical Efficacy Results from the Placebo-Controlled Study

	Baseline, Mean (SD)		Change from Baseline to Month 18, LS Mean (SEM)		Patisiran-Placebo Treatment Difference,	
Endpoint	Patisiran N=148	Placebo N=77	Patisiran	Placebo	LS Mean (95% CI)	p-value
Primary						
mNIS+7	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0 (-39.9, -28.1)	p<0.001
Secondary						
Norfolk QoL-DN	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	p<0.001
10-meter walk test (m/sec)	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	p<0.001
mBMI	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	p<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:

Initiation of patisiran (Onpattro) **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. Inotersen (Tegsedi)
    b. Tafamidis meglumine (Vyndaqel)
    c. Tafamidis (Vyndamax)
7. Patisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis
8. Dose does not exceed the following:
    a. Weight less than 100 kg: 0.3 mg/kg (up to 30 mg) once every 3 weeks
    b. Weight greater than 100 kg: 30 mg once every 3 weeks

Approval duration: 1 year

Continuation of patisiran (Onpattro) **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. Inotersen (Tegsedi)
    b. Tafamidis meglumine (Vyndaqel)
    c. Tafamidis (Vyndamax)
7. Patisiran is prescribed by (or in consultation with) a neurologist, geneticist, or physician specializing in the treatment of amyloidosis

8. Dose does not exceed the following:
    a. Weight less than 100 kg: 0.3 mg/kg (up to 30 mg) once every 3 weeks
    b. Weight greater than 100 kg: 30 mg once every 3 weeks

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

- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.
- For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.
- Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:
    - Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
    - Oral acetaminophen (500 mg)
    - Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
    - Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)

Dose Adjustments

None

Drug Availability

Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) white to off-white, opalescent, homogeneous solution in a single-dose vial.

PRECAUTIONS:

Boxed Warning

None

Contraindications

None

Precautions/Warnings

- Infusion related reactions
- Reduced serum vitamin A levels and recommended supplementation

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0222	Injection, Patisiran, 0.1 mg

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: BCBSF 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.

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:

Inotersen (Tegsedi)

OTHER:

None

REFERENCES:

1. Adams D, Gonzalex-Duarte A, O'Riodan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):11-21.
2. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017 Sep 11;17(1):181
3. Akcea Therapeutics. Tegsedi (inotersen) injection. 2018 [cited 9/29/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8513207e-b55f-417b-9473-af785146a543/.
4. Alnylam Pharmaceuticals. Onpattro (patisiran) injection. 2018 [cited 9/29/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e87ec36f-b4b4-49d4-aea4-d4ffb09b0970/.
5. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):22-31.
6. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2015 [cited 9/29/19]. Available from: http://www.clinicalpharmacology.com/.
7. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 9/29/19]. Available from: http://clinicaltrials.gov/.
8. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 9/29/19]. Available from: http://www.thomsonhc.com/.
9. Maurer MS, Schartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-1016.
10. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2015 [cited 9/29/19]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 10/9/19.

GUIDELINE UPDATE INFORMATION:

12/15/18	New Medical Coverage Guideline.
01/01/19	Revision: HCPCS code updates. Added C9036.
11/15/19	Review and revision, consisting of updating references, position statement, description