ONPATTRO® (PATISIRAN)

Policy Number: CS2020D0072G **Effective Date**: TBD

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Commercial Policy
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APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana

COVERAGE RATIONALE

Onpattro® (patisiran) is proven and medically necessary for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in patients who meet ALL of the following criteria:[1,8]

- For initial therapy, **all** of the following:
  - **Both** of the following:
    - Diagnosis of hATTR amyloidosis with polyneuropathy
    - Documentation that the patient has a pathogenic TTR mutation (e.g., V30M);

    and
  - Prescribed by or in consultation with a neurologist; **and**
  - Documentation of **one** of the following:
    - Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
    - Patient has a baseline FAP Stage 1 or 2;

    and
  - Patient has not had a liver transplant; **and**
  - Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **and**
  - Patient is not receiving Onpattro in combination with either of the following:
    - Oligonucleotide agents [e.g., Tegsedi (inotersen)]
    - Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis);

    and
  - Patisiran dosing is in accordance with the U.S. Food and Drug Administration prescribing information (0.3 mg/kg up to a maximum of 30mg, every 3 weeks); **and**
  - Initial authorization is for no more than 12 months

- For continuation therapy, **all** of the following:

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- Patient has previously received treatment with Onpattro; **and**
- Prescribed by or in consultation with a neurologist; **and**
- Documentation of **one** of the following:
  - Patient continues to have a polyneuropathy disability (PND) score ≤ IIIb
  - Patient continues to have a FAP Stage 1 or 2;

  and
- Documentation that the patient has experienced a positive clinical response to Onpattro (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **and**
- Patient is not receiving Onpattro in combination with either of the following:
  - Oligonucleotide agents [e.g., Tegsedi (inotersen)]
  - Vyndaqel (tafamidis meglumine) or Vyndamax (tafamidis);

  and
- Patisiran dosing is in accordance with the U.S. Food and Drug Administration prescribing information (0.3 mg/kg up to a maximum of 30mg, every 3 weeks); **and**
- Authorization is for no more than 12 months

Onpattro® (patisiran) is unproven and not medically necessary for the treatment of:
- Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis
- Primary or leptomeningeal amyloidosis

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0222	Injection, patisiran, 0.1 mg

ICD-10 Diagnosis Code	Description
E85.1	Neuropathic heredofamilial amyloidosis

BACKGROUND

Hereditary ATTR (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy, is a progressive, disabling and life-threatening polyneuropathy affecting the peripheral and autonomic nervous system. This disease is an autosomal transmission disorder which is usually due to a point mutation of the transthyretin (TTR) gene. The disease is caused by misfolded transthyretin (TTR) protein that accumulates as amyloid fibrils in multiple organs, including the nerves, heart, and gastrointestinal tract.

Onpattro (patisiran) is a double-stranded small interfering RNA (siRNA) that targets a sequence of mRNA conserved across wild-type and all TTR variants and can thereby degrade and reduce serum levels and protein deposits in tissues of both wild-type and mutated protein. It is formulated as lipid nanoparticles which direct it to the liver, the primary source of circulating TTR. Patisiran therapy is associated with observed lowering of TTR levels in both wild-type and mutant (V30M) forms of TTR.

A genetic testing service is available in the United States and Canada and a genetic counseling service is available in the United States. Medical professionals and patients may access information on the Alnylam Pharmaceuticals website.

CLINICAL EVIDENCE

A randomized, double-blind, placebo-controlled, phase III, global study (APOLLO) evaluated the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy. 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 2:1 (N=148:77) to receive either intravenous (IV) patisiran 0.3 mg/kg or placebo every 3 weeks. The primary endpoint was to determine the efficacy of patisiran at 18 months based on the difference in the change in modified NIS+7 (a composite measure of motor strength, sensation, reflexes, nerve conduction, and autonomic function) between the patisiran and placebo groups. Secondary endpoints evaluated the effect of patisiran on Norfolk-Diabetic Neuropathy quality of life questionnaire score, nutritional status (as evaluated by modified body mass index), motor function (as measured by NIS-weakness and

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timed 10-m walk test), and autonomic symptoms (as measured by the Composite Autonomic Symptom Score-31 questionnaire). Exploratory objectives include assessment of cardiac function and pathologic evaluation to assess nerve fiber innervation and amyloid burden. Safety of patisiran was also assessed throughout the study. 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. These reactions decreased over time and led to treatment discontinuation in only 1 patient. The investigators concluded that patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo while significantly reducing disease symptoms and disability, improvement in quality of life, nutritional status, strength, and ambulation seen with patisiran relative to placebo.[1,8]

In a subpopulation analysis of the APOLLO trial, investigators evaluated the threatment association of patisiran with regional left ventricular (LV) myocardial strain in cardiac manifestation in hATTR.[11,12] The prespecified cardiac subpopulation (126 of 225 [56%]) comprised of patients with a baseline LV wall thickness of 13 mm or more and no history of hypertension or aortic valve disease. Of the 126 patients included in the prespecified cardiac subpopulation, 36 patients (28.6%) received placebo and 90 patients (71.4%) received patisiran. At baseline, LV global longitudinal strain (GLS) was impaired and regional longitudinal strains were lowest in the basal segments with apical sparing. There were no differences in regional longitudinal strains between the treatment groups at baseline. Patisiran improved the absolute GLS (least-squares mean [SE] difference, 1.4% [0.6%]; 95% CI, 0.3%-2.5%; P = .02) compared with placebo at 18 months, with the greatest differential increase observed in the basal region (overall least-squares mean [SE] difference, 2.1% [0.8%]; 95% CI, 0.6%-3.6%; P = .006) and no significant differences in the mid and apical regions among groups. Patisiran reduced mean left ventricular wall thickness (least-squares mean difference ± SEM: −0.9±0.4 mm, P=0.017), interventricular septal wall thickness, posterior wall thickness, and relative wall thickness at month 18 compared with placebo. Patisiran also led to increased end-diastolic volume (8.3±3.9 mL, P=0.036), decreased global longitudinal strain (−1.4±0.6%, P=0.015), and increased cardiac output (0.38±0.19 L/min, P=0.044) compared with placebo at month 18. Patisiran lowered N-terminal prohormone of brain natriuretic peptide at 9 and 18 months (at 18 months, ratio of fold-change patisiran/placebo 0.45, P<0.001). A consistent effect on N-terminal prohormone of brain natriuretic peptide at 18 months was observed in the overall APOLLO patient population (n=225). Median follow-up duration was 18.7 months. The exposure-adjusted rates of cardiac hospitalizations and all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively (Andersen–Gill hazard ratio, 0.54; 95% CI, 0.28–1.01). The authors concluded that patisiran prevented the deterioration of LV GLS and decreased mean LV wall thickness over 18 months, suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis.

Institute for Clinical and Economic Review (ICER)
On October 4th, 2018, ICER released a clinical report entitled, "Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value". ICER recommendations are as follows:13
- **ICER judges the clinical evidence for patisiran to be "incremental" or "better".**
- **On average, patients on patisiran demonstrated improvement in neuropathy symptoms, as measured by the mNIS+7. Based on the current body of evidence, there is moderate certainty of a substantial net health benefit with high certainty of at least a small net health benefit compared to best supportive care.**

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for ONPATTRO® (patisiran). Local Coverage Determinations (LCDs) do not exist.

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In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed ~~April 11, 2019~~ **June 30, 2020**)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	**Annual review. No changes to coverage rationale. Updated Clinical Evidence, CMS statement, and references.**

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