ONPATTRO™ (PATISIRAN)

Policy Number: PHARMACY 312.1 T2 **Effective Date**: September 1, 2018

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Related Policy

- Review at Launch for New to Market Medications

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	No[1]
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	[1]We strongly recommend that you request precertification for this medication. While no penalty will be imposed for failure to request a pre-service review, if you do not request one, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the

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Special Considerations *(continued)*	medication. As of **Jan. 1, 2019**, precertification will be required. Refer to the policy titled Review at Launch for New to Market Medications.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Onpattro (patisiran) is proven for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis.

Onpattro (patisiran) is medically necessary for the treatment of the polyneuropathy of 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
  - 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
  - Presence of clinical signs and symptoms of the disease (e.g., peripheral/autonomic neuropathy, motor disability, cardiovascular dysfunction, renal dysfunction); **and**
  - Patient is not receiving patisiran in combination with either of the following:
    - Oligonucleotide agents (e.g., inotersen)
    - Tafamidis meglumine

    and
  - Patisiran dosing is in accordance with the US 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:
  - Patient has previously received treatment with patisiran; **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 patisiran (e.g., improved neurologic impairment, motor function, cardiac function, quality of life assessment, serum TTR levels, etc.); **and**
  - Patient is not receiving patisiran in combination with either of the following:
    - Oligonucleotide agents (e.g., inotersen)
    - Tafamidis meglumine

    and
  - Patisiran dosing is in accordance with the US 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.

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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

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.

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

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 the member specific benefit plan document 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 may apply.

HCPCS Code	Description
C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J3490	Unclassified drugs

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

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 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

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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]

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [*2018D0072A*]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
09/11/2018	• Corrected textual error; removed repetitive language/duplicate reference to "with polyneuropathy" from medical necessity statement
09/01/2018	• New policy

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