POLICY: Amyloidosis – Onpattro (patisiran intravenous injection – Alnylam)

APPROVAL DATE: 10/16/2019

OVERVIEW

Onpattro is a lipid nanoparticle formulated RNA interference (RNAi) therapeutic indicated for treatment of hereditary amyloid transthyretin amyloidosis (hATTR) with polyneuropathy.[1] hATTR is a rare, inherited, rapidly-progressive, debilitating, life-threatening disease.[2-4] It is a multisystem condition caused by mutation in the transthyretin (TTR) gene that results in misfolded TTR protein accumulation (as amyloid) in the nerves, heart, and other areas of the body. Onpattro targets hepatic production of mutant TTR. By reducing the unstable circulating TTR tetramers, organ deposition of amyloid is prevented, thus, stabilizing or improving symptoms of neuropathy.

Guidelines

There is a European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016). Symptomatic management associated with sensory-motor neuropathy and autonomic dysfunction should be started at diagnosis.[3] This may include painkillers, antidiarrheal drugs, treatment of symptomatic orthostatic hypotension, diuretics for heart failure, prophylactic pacemaker implantation for conduction disorders, and/or vitrectomy/trabeculectomy for ocular amyloidosis or glaucoma. Tetramer stabilizers (tafamidis and diflunisal) are mentioned as treatment options that slow the rate of amyloidogenesis by preventing the dissociation, misfolding, and misassembly of mutated TTR. Tafamidis is recommended for use in patients with Stage 1 disease. Those presenting with Stage 2 disease are recommended for a clinical trial with an antisense oligonucleotide, small interfering RNA, doxycycline-tauroursodeoxycholic acid, or off-label use of diflunisal. For symptomatic relief of neuropathic pain due to hATTR, pregabalin, gabapentin, amitriptyline, and duloxetine are potential treatments.[5,6]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Onpattro. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Onpattro as well as the monitoring required for adverse events and long-term efficacy, approval requires Onpattro to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the approval duration noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) The patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND

B) The patient has symptomatic peripheral neuropathy.
Note: Examples of symptomatic peripheral neuropathy include reduced motor strength/ coordination, impaired sensation (e.g., pain, temperature, vibration, touch); AND

C) The patient 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, duloxetine, or a tricyclic antidepressant.
Note: Examples of gabapentin-type products include gabapentin (Neurontin) and pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline; AND

D) The patient is 18 years of age or older; AND

E) Onpattro is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

Dosing. Approve the following dosing (A and B):

A) The dose is up to 0.3 mg/kg IV givenintravenously up to a maximum dose of 30 mg; AND

B) The dose is administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Concomitant Use With Tegsedi (inotersen subcutaneous injection) or a Tafamidis Product.** Note: examples of tafamadis products are Vynaqel and Vyndamax. There are insufficient data supporting the safety and efficacy of concurrent use of these agents for ATTR-PN. The Vyndaqel/Vyndamax pivotal trial, which took place prior when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Onpattro and Tegsedi did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal).

2. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Onpattro lipid complex injection, for intravenous use [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; September 2019.
2. Rizk M, Tüzmen Ş. Update on the clinical utility of an RNA interference-based treatment: focus on patisiran. *Pharmgenomics Pers Med*. 2017;10:267-278.
3. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29 Suppl 1:S14-26.
4. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol.* 2015;66(21):2451-2466.
5. Ando Y, Coelho T, Berk JL. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
6. Kristen AV, Ajroud-Driss S, Conceição I, et al. Patisiran, an RNAi therapeutic for the treatment of hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2019;9(1):5-23.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New Policy	--	08/15/2018
Early annual revision	**Polyneuropathy of hATTR:** Add criteria to require patients to have tried or be currently taking a gabapentin-type product or a TCA.	10/03/2018
revision	**Polyneuropathy of hATTR:** Remove the word "documentation" from criterion that requires genetic testing for the TTR mutation. This edit is intended to clarify that documentation is not required to be submitted for approval.	10/30/2018
Annual revision	**Polyneuropathy of hATTR:** The dose was clarified to be up to the maximum dose and shortest treatment interval. Duloxetine was added as a systemic agent that may be tried prior to Onpattro. **Conditions Not Recommended for Approval:** Concomitant use with Tegsedi or tafamidis products was added to the list of conditions not recommended for coverage.	10/16/2019