Washington State Health Care Authority

Psychotherapeutic and Neurological Agents – MISC : Transthyretin Amyloidosis Agents

Medical policy no. 62.70.00-1 Effective Date: July 1, 2019

Background:

Hereditary transthyretin-mediated amyloidosis (hATTR) is a progressive disease caused by deposits of misfolded transthyretin (TTR) protein. The disorder most commonly presents as primarily neurologic symptoms, cardiac symptoms, or a combination of the two primary phenotypes. The neurologic phenotype was previously referred to as familial amyloid polyneuropathy or FAP and is now called hATTR polyneuropathy. Diagnosis with this disease is rare – about 10,000 people worldwide and 3,000-3,500 people in the United States have received a hATTR polyneuropathy diagnosis.

Prior to the approval of Onpattro (patisiran) and Tegsedi (inotersen), the goal of treatment was symptom alleviation. Onpattro was the first FDA-approved treatment for patients with hATTR polyneuropathy, which changed the treatment focus to the cause of the disorder – the production of misfolded protein. Tegsedi was also approved by the FDA to treat polyneuropathy that hATTR patients suffer from by breaking down mutant and wild-type TTR.

Medical necessity:

Drug	Medical Necessity
Onpattro (patisiran)	Onpattro may be considered medically necessary when used for the following conditions: 1. hATTR polyneuropathy
Tegsedi (inotersen)	Tegsedi may be considered medically necessary when used for the following conditions: 1. hATTR polyneuropathy

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
Onpattro (patisiran)	Onpattro may be covered when ALL of the following are met: 1. Patient is 18 years of age or older; **AND** 2. Patient has a diagnosis hATTR polyneuropathy (or FAP) as documented by evidence of polyneuropathy and pathogenic TTR variant using molecular genetic testing; **AND** 3. Documentation of baseline disease severity using Neuropathic Impairment Score (NIS) OR Polyneuropathy Disability (PND); **AND** 4. Documentation of baseline disease severity as evidenced by other measurable factors (e.g., quality of life, motor strength, disability, gait speed, etc.); **AND**

	5. Drug is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis; **AND** 6. Patient is not currently taking Tegsedi, difunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; **AND** 7. Patient has no history of or planned future liver transplant; **AND** 8. Patient does not have severe renal impairment, end-stage renal disease, or moderate-severe hepatic impairment. If ALL criteria are met, the request will be approved for 12 months
	Criteria (Reauthorization)
	Onpattro may be continued when ALL of the following are met: 1. Documentation of positive clinical response as provided by NIS score, PND score, or other baseline measures of function If ALL criteria are met, the request will be approved for 12 months
Drug	**Clinical Criteria (Initial Approval)**
Tegsedi (inotersen)	Tegsedi may be covered when ALL of the following are met: 1. Patient is 18 years of age or older; **AND** 2. Patient has a diagnosis hATTR polyneuropathy (or FAP) as documented by evidence of polyneuropathy and pathogenic TTR variant using molecular genetic testing; **AND** 3. Documentation of baseline disease severity using Neuropathic Impairment Score (NIS) OR Polyneuropathy Disability (PND); **AND** 4. Documentation of baseline disease severity as evidenced by other measurable factors (e.g., quality of life, motor strength, disability, gait speed, etc.); **AND** 5. Drug is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis; **AND** 6. Patient is not currently taking Onpattro, difunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; **AND** 7. Patient has no history of or planned future liver transplant; **AND** 8. Patient does not have severe renal impairment, end-stage renal disease, or moderate-severe hepatic impairment. If ALL criteria are met, the request will be approved for 12 months
	Criteria (Reauthorization)
	Tegsedi may be continued when ALL of the following are met: 1. Documentation of positive clinical response as provided by NIS score, PND score, or other baseline measures of function If ALL criteria are met, the request will be approved for 12 months

Dosage and quantity limits:

Drug Name	Dose and Quantity Limits
Onpattro (patisiran)	Weight-based dosing: o Less than 100 kg: 0.3 mg/kg every 3 weeks o Patients weighing 100 kg or more: 30 mg every 3 weeks
Tegsedi (inotersen)	284 mg SQ injection every week

Coding:

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

Evidence review:

Onpattro (patisiran):

Onpattro efficacy was evaluated in a randomized, double-blind, placebo-controlled trial in adults with hATTR polyneuropathy. Patients were randomized to receive intravenous Onpattro (patisiran) at a dose of 0.3 mg/kg (n = 148) or placebo (n = 77) once every 3 weeks for 18 months. All patients received a corticosteroid, acetaminophen, and antihistamines before treatment.

The primary efficacy endpoint studied was the change from baseline at month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7), which measures deficits in cranial nerve function, muscle strength, reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The maximum mNIS+7 score was 304, with higher scores associated with greater disease severity.

The clinical meaningfulness of changes in the objective mNIS+7 scale was assessed by the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, a patient-reported metric that asks for input on physical functioning, large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. In the study, the change in Qol-DN score from baseline to month 18 was evaluated.

The mean mNIS+7 and QoL-DN scores were similar at baseline in both groups. The mean mNIS+7 score decreased by 6.0 points while the score increased by 34.0 points in the placebo group during the study period ($p<0.001$). The mean QoL-DN score decreased by 6.7 points in the treatment group while the mean score increased by 14.4 points in the placebo group during the study period ($p<0.001$). Onpattro demonstrated statistically and clinically significant differences from placebo for both scores.

Tegsedi (inotersen):

A randomized, double-blind, placebo-controlled trial was conducted in adult patients with hATTR polyneuropathy to determine the efficacy of Tegsedi. Patients were randomized to receive 284 mg SQ of Tegsedi weekly (n=113) or placebo (n=60) for 66 weeks. The endpoint studied were the change from baseline to week 66 in the mNIS+7 scale and the total QoL-DN score.

There was a significant difference in the change from baseline in the mNIS+7 scores in the treatment group compared to placebo (5.8 vs 25.2; $p<0.001$). There was a significant difference in the change from baseline in the the Qol-DN scores in the treatment group compared to the placebo group (1.0 vs 12.7; $p<0.001$). These differences demonstrate the efficacy of Tegsedi used to treat polyneuropathy caused by hATTR amyloidosis.

References

1. Ando, Yukio, et al. "Guideline of transthyretin-related hereditary amyloidosis for clinicians." *Orphanet journal of rare diseases* 8.1 (2013): 31.

2. Adams, David, 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 neurology* 17.1 (2017): 181.
3. Onpattro [prescribing information]. San Diego, CA: Alnylam Pharmaceuticals, Inc.; 2018.
4. Tegsedi injection [prescribing information]. Carlsbad, CA: Ionis/Akcea Therapeutics; 2018.
5. 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.
6. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. J Am Coll Cardiol. 2015;66(21):2451-2466.
7. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. New England Journal of Medicine. 2018May;379(1):22–31.
8. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Institute for Clinical and Economic Review. August 29, 2018

History

Date	Action and Summary of Changes
05.06.2019	New Policy