PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tegsedi Utilization Review Medical Policy
- Tegsedi® (inotersen injection for subcutaneous use – Ionis/Akcea Therapeutics)

REVIEW DATE: 10/28/2020

OVERVIEW

Tegsedi, an antisense oligonucleotide indicated for treatment of adults with **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)**.[1] hATTR is a rare, inherited, rapidly-progressive, debilitating, life-threatening disease.[2-3] 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. Tegsedi binds to TTR messenger RNA, causing degradation of mutant and wild-type TTR mRNA. This reduces serum TTR protein and TTR protein deposits in tissues.[1]

Guidelines

A European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016) was published prior to approval of Tegsedi and Onpattro.[2] Symptomatic management associated with sensory-motor neuropathy and autonomic dysfunction should be started at diagnosis. 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 the clinical symptoms associated with neuropathic pain due to hATTR, pregabalin, gabapentin, amitriptyline, and duloxetine are potential treatments.[5,6] Prior to the availability of drug therapies, liver transplantation (which removes the main source of mutated TTR) was the only treatment option for hATTR.[2]

Safety

Tegsedi has a Boxed Warning regarding sudden and unpredictable thrombocytopenia which may be life-threatening.[1] It is contraindicated in patients with a platelet count less than 100 x 10^9/L. Based on monitoring, Tegsedi may need to be interrupted or discontinued. Following discontinuation, continue to monitor platelet counts for 8 weeks (or longer if platelet count is less than 100 x 10^9/L). Tegsedi also has a Boxed Warning regarding glomerulonephritis, which may require immunosuppressive treatment and may lead to dialysis-dependent renal failure. Due to the risks and frequent monitoring for both serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, Tegsedi is only available through a restricted distribution program under the Tegsedi REMS (Risk Evaluation and Mitigation Strategy).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tegsedi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tegsedi as well as the monitoring required for adverse events and long-

term efficacy, approval requires Tegsedi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tegsedi 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, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** 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; AND
     Note: Examples of gabapentin-type products include gabapentin (Neurontin) and pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline.
   - **E)** Patient does not have a history of liver transplantation; AND
   - **F)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Tegsedi is not recommended in the following situations:

1. **Concomitant Use With Onpattro (patisiran lipid complex intravenous infusion) or a Tafamidis Product.** Note: Examples of tafamidis products are Vyndaqel 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). There is a Phase II open-label extension study (n = 27) using Onpattro that included 13 patients who were treated concomitantly with tafamidis.[7] Following 24 months of treatment, there was no significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%).

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. Tegsedi injection [prescribing information]. Carlsbad, CA: Ionis/Akcea Therapeutics; July 2020.
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3. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol*. 2015;66(21):2451-2466.
4. Onpattro injection [prescribing information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; September 2019.
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.
7. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.