



**POLICY:** Amyloidosis – Tegsedi™ (inotersen injection for subcutaneous use – Ionis/Akcea Therapeutics)

**APPROVAL DATE:** 10/16/2019

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## OVERVIEW

Tegsedi is an antisense oligonucleotide indicated for treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR).<sup>1</sup> hATTR is a rare, inherited, rapidly-progressive, debilitating, life-threatening disease.<sup>2-3</sup> 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.<sup>1</sup>

## Guidelines

A European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016) was published prior to approval of Tegsedi and Onpattro.<sup>2</sup> 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.<sup>5,6</sup>

## Safety

Tegsedi has a Boxed Warning regarding sudden and unpredictable thrombocytopenia which may be life-threatening.<sup>1</sup> It is contraindicated in patients with a platelet count less than  $100 \times 10^9/L$ . Platelets should be monitored prior to starting therapy and during treatment as directed in the prescribing information. Do not administer to any patient with signs or symptoms of thrombocytopenia unless results are interpretable and acceptable to a medical professional. 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  $100 \times 10^9/L$ ). 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 a the Tegsedi REMS (Risk Evaluation and Mitigation Strategy).

## POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Tegsedi. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. 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 Tegsedi as well as the

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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. All approvals are provided for the approval duration noted below.

## RECOMMENDED AUTHORIZATION CRITERIA

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

### FDA-Approved Indication

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

**Dosing.** Approve 284 mg subcutaneously once weekly.

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tegsedi 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 Onpattro (patisiran lipid complex intravenous infusion) or a Tafamidis Product.** Note: examples of tafamidis 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. Tegsedi injection [prescribing information]. Carlsbad, CA: Ionis/Akcea Therapeutics; October 2018.
2. 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.
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.

## HISTORY

Type of Revision	Summary of Changes	Approval Date
New Policy	--	10/10/2018
revision	<b>Polyneuropathy of hATTR:</b> 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	<b>Polyneuropathy of hATTR:</b> Duloxetine was added as a systemic agent that may be tried prior to Tegsedi. <b>Conditions Not Recommended for Approval:</b> Concomitant use with Onpattro or tafamidis products was added to the list of conditions not recommended for coverage.	10/16/2019