inotersen (Tegsedi™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO039

Description

Inotersen (Tegsedi) is a subcutaneously administered antisense oligonucleotide inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

inotersen (Tegsedi)	Indication	Quantity Limit	*DDID*
284 mg/1.5 mL syringe	hereditary transthyretin-mediated amyloidosis	6 mL/28 days	204500

Initial Evaluation

I. Inotersen (Tegsedi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by or in consultation with a neurologist or cardiologist; **AND**
   B. A diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) when the following are met:
      1. Age 18 years and older; **AND**
      2. Documented transthyretin variant (TTR mutation) by genotyping (e.g., V30M); **AND**
      3. Documented amyloid deposit by biopsy; **AND**
      4. Patient has a platelet count > 100 × 109/L; **AND**
      5. Documentation of one of the following:
         i. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
         ii. Patient has a baseline FAP Stage 1 or 2
         iii. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

         AND
      6. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **AND**
      7. No prior liver transplant or anticipated liver transplant; **AND**
      8. New York Heart Association (NYHA) functional classification of <3; **AND**
      9. Does not have presence of known type 1 or type 2 diabetes mellitus; **AND**
      10. Does not have renal insufficiency (defined as CrCl <60 mL/min); **AND**
      11. Patient has tried and failed or has a contraindication to patisiran (Onpattro); **AND**

12. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel)

II. Inotersen (Tegsedi) is considered investigational when used for all other conditions, including but not limited to:
   A. Cardiac amyloidosis due to wild-type or mutant TTR

Renewal Evaluation

I. Patient has previously received treatment with inotersen (Tegsedi); **AND**
II. Documentation of one of the following:
   A. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb; **OR**
   B. Patient has a baseline FAP Stage 1 or 2; **OR**
   C. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

   AND
III. Documentation that the patient has experienced a positive clinical response to inotersen (Tegsedi) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**
IV. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**
V. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. In the pivotal NEURO-TTR trial leading to approval, inotersen (Tegsedi) was studied in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy.
II. Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related *TTR* gene mutations; thus, DNA sequencing is usually required.
III. Use of inotersen (Tegsedi) is contraindicated in patients with platelet count less than 100 x 109/L, history of acute glomerulonephritis caused by inotersen (Tegsedi), or history of hypersensitivity reaction to inotersen (Tegsedi).
IV. Patients with a PND score greater than IIIb (i.e. PND of IV) are confined to a wheelchair or bedridden. Patients with FAP stage 1 have unimpaired ambulation, stage 2 require assistance with ambulation, and FAP stage 3 patients are wheelchair bound or bedridden. As mentioned above, all patients included in the study were ambulatory. Patents included also had a baseline NIS score ≥ 10 and ≤ 130.

V. Additional exclusion criteria in the NEURO-TTR trial consisted of prior liver transplant or anticipated liver transplant, New York Heart Association (NYHA) functional classification of <3, presence of known type 1 or type 2 diabetes mellitus, and renal insufficiency (defined as CrCl <60 mL/min).

VI. Inotersen (Tegsedi) carries two black box warnings related to potential for life-threatening thrombocytopenia and glomerulonephritis that may require immunosuppressive treatment and may result in dialysis. Tegsedi is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program because of these risks. Patisiran (Onpattro) is also indicated and FDA approved for the polyneuropathy of hATTR in adults and provides a more favorable safety profile. Onpattro efficacy was evaluated in a randomized, double-blind, placebo-controlled trial in adults with polyneuropathy caused by hATTR amyloidosis. Onpattro met its primary endpoint of change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7).

VII. Use of inotersen (Tegsedi) in combination with other therapies for hATTR (e.g., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel) has not been studied.

Investigational or Not Medically Necessary Uses

I. Cardiac amyloidosis due to wild-type or mutant TTR
   A. Pivotal trials leading to FDA approval were specifically in the hereditary transthyretin-mediated amyloidosis setting. Wild-type TTR is not considered hereditary. Inotersen (Tegsedi) in this setting is under investigation, trials have not yet started recruiting.

References

1. Tegsedi [Prescribing Information]. Carlsbad, CA: Ionis Therapeutics, Inc., 2018.
2. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. NEJM. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153.
3. Buxbaum J. Oligonucleotide Drugs for Transthyretin Amyloidosis. NEJM. 2018;379(1):82-85. doi:10.1056/NEJMe1805499.
4. Gonzalez-Duarte A, Adams D, O'Riordan W, et al. Changes in Neuropathy Stage in Patients with Hereditary Transthyretin-Mediated Amyloidosis Following Treatment with Patisiran, an Investigational RNAi Therapeutic: An Analysis from the Phase 3 APOLLO Study. Available at: http://www.alnylam.com/wp-content/uploads/2018/03/5.-APOLLO-PND-FAP_FINAL.pdf.
5. Center for Drug Evaluation and Research. Tegsedi (inotersen) Summary Review. Application Number: 211172Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211172Orig1s000SumR.pdf
6. Benson MD, Waddington-cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31.
7. Coelho T, Ericzon B, Falk R, et al. A Guide to Transthyretin Amyloidosis. Available at: http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf.
8. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8(1):1-18. doi:10.1186/1750-1172-8-31.

Policy Implementation/Update:

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Last Updated	
Last Reviewed	

Action and Summary of Changes	Date