Clinical Criteria

Subject:	Tegsedi (inotersen)		
Document #:	ING-CC-0084	**Publish Date**:	~~09/23/2019~~09/21/2020
Status:	Revised	**Last Review Date**:	~~08/16/2019~~08/21/2020

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Overview

This document addresses the use of Tegsedi (inotersen), an antisense oligonucleotide approved by the Food and Drug Administration (FDA) for the treatment of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. hATTR amyloidosis was formerly known as familial amyloid polyneuropathy (FAP).

Hereditary transthyretin (hATTR) amyloidosis is a multisystemic, progressive, life-threatening disease characterized by extracellular deposition of amyloid fibrils composed of misfolded transthyretin (TTR), a plasma transport protein produced predominantly by the liver. Amyloid fibrils accumulate in various organs and tissues including the heart, kidney, gastrointestinal tract, and peripheral nerves, resulting in clinical manifestations such as polyneuropathy and cardiomyopathy. Potential symptoms associated with hATTR amyloidosis include but are not limited to muscle weakness, difficulty ambulating, impaired balance, orthostatic hypotension, disturbances in GI mobility, heart failure, arrhythmias and sudden death due to severe conduction disorders.

Due to the constellation of symptoms and multisystemic nature of the disease, various assessments need to be utilized in an effort to quantify the overall disease burden for each individual with hATTR amyloidosis. Examples of clinical tests include the Neuropathy Impairment Score (NIS) and Polyneuropathy Disability (PND) Score. Clinical trials evaluated the use of Tegsedi in individuals with hATTR amyloidosis and mild to moderate polyneuropathy. An example of mild to moderate polyneuropathy status is an individual who is able to ambulate with or without the use of assistance.

The efficacy of Tegsedi was demonstrated in a randomized, double-blind, placebo-controlled trial in 172 adults with stage 1 (ambulatory) or stage 2 (ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy. Study participants had a Neuropathy Impairment Score (NIS) of 10-130 (NIS scale ranges from 0-244), a TTR mutation confirmed by genotyping and amyloid deposits documented on biopsy. Key exclusion criteria were previous liver transplant, New York Heart Association (NYHA) class III or IV heart failure, severe renal impairment or end-stage renal disease, moderate or severe hepatic impairment and other causes of polyneuropathy unrelated to hATTR amyloidosis. Both primary efficacy assessments favored Tegsedi over placebo. The difference in least-squares mean change from baseline to week 66 between groups was −19.7 points (95% CI −26.4 to −13.0) for the standardized modified Neuropathy Impairment Score+7 (mNIS+7) composite score and −11.7 points (95% CI −18.3 to −5.1) for the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire.

Treatment with Tegsedi leads to a decrease in serum vitamin A levels. Individuals should be advised to take vitamin A supplementation at the recommended daily allowance while receiving Tegsedi therapy.

Tegsedi has black box warnings for thrombocytopenia and glomerulonephritis. Tegsedi causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia and is contraindicated in individuals with a platelet count below 100 x 10^9/L at baseline. During treatment, platelet counts should be monitored weekly if values are 75 x 10^9/L or greater and more frequently if values are less than 75 x 10^9/L. Following discontinuation of therapy, platelet counts should be monitored for 8 weeks or longer to verify values remain above 75 x 10^9/L. Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. Tegsedi should not be initiated in individuals with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher. Serum creatinine, estimated glomerular filtration rate (eGFR) and UPCR should be monitored at baseline and every two weeks during treatment. Tegsedi should not be administered to individuals who develop a UPCR of 1000 mg/g or higher or eGFR below 45 mL/min/1.73 m^2, pending further evaluation. The FDA has required the manufacturer to develop a comprehensive risk

management program that includes the enrollment of prescribers in the Tegsedi Risk Evaluation and Mitigation Strategy (REMS) Program. Additional information and forms for individuals, prescribers and pharmacists may be found at www.tegsedirems.com.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Tegsedi (inotersen)

Initial ~~R~~requests for Tegsedi (inotersen) may be approved if the following criteria are met:

I. Individual has a diagnosis of hereditary transthyretin (hATTR) amyloidosis or familial amyloid polyneuropathy (FAP); **AND**
II. Individual has a TTR mutation confirmed by genotyping (Benson, 2018); **AND**
III. Individual has associated mild to moderate polyneuropathy (Benson, 2018); **AND**
IV. Individual has a baseline platelet count greater than or equal to 100 x 10^9/L; **AND**
V. Individual has a urinary protein to creatinine ratio (UPCR) less than 1000 mg/g.

Continuation requests for Tegsedi (inotersen) may be approved if the following criteria are met:

I. There is documentation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improved ambulation, improvement in neurologic symptom burden, improvement in activities of daily living); **AND**
II. Individual's most recent platelet count was within the past month and was greater than or equal to 100 x 10^9/L; **AND**
III. Individual's most recent urinary protein to creatinine ratio (UPCR) was within the past month and was less than 1000 mg/g.

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Requests for Tegsedi (inotersen) may not be approved for the following:

I. All other indications not included above; **OR**
II. Individual has a history of liver transplantation; **OR**
III. Individual has severe renal impairment or end-stage renal disease; **OR**
IV. Individual has a history of acute glomerulonephritis caused by Tegsedi; **OR**
V. Individual has moderate or severe hepatic impairment; **OR**
VI. Individual has New York Heart Association (NYHA) class III or IV heart failure (Benson, 2018); **OR**
VII. Individual has sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.) (Benson, 2018); **OR**
VIII. Individual is using in combination with Onpattro, Vyndaqel or Vyndamax.

Quantity Limits

Tegsedi (inotersen) Quantity Limit

Drug	Limit
Tegsedi (inotersen) 284 mg/1.5 mL prefilled syringe	4 syringes per 28 days

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY) [when specified as Tegsedi]
J3490	Unclassified drugs [when specified as Tegsedi]

ICD-10 Diagnosis

E85.1-E85.9	Neuropathic heredofamilial amyloidosis
G62.9	Polyneuropathy, Unspecified

Document History

Revised: 8/21/2020
Document History:

- 8/21/2020 – Annual Review: Add continuation criteria to Tegsedi clinical criteria. Administrative update to add drug specific quantity limit.Coding reviewed: No changes
- 08/16/2019 – Annual Review: Add may not approve criteria for combination use with other agents for amyloidosis. Wording and formatting changes. Coding Reviewed: Added ICD-10 E85.9, and G62.9.
- 12/4/2018 – HCPCs and ICD-10 Coding Review: Add HCPCS C9399 and ICD-10 E85.1.
- 10/9/2018 – Select Review: Add clinical criteria for Tegsedi following FDA approval.
- 08/17/2018 – Annual Review: Review preliminary clinical criteria for inotersen.

References

1. Ando Y, Coelho T, Berk JL, et. al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8(31).
2. 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.
3. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 3, 2020.
4. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
5. Gertz MA, Benson MD, Dyck PJ, et. al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. *J Am Coll Cardiol*. 2015;66(21):2451-2466.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2020; Updated periodically.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.