Effective Date **4/1/2024**
Coverage Policy Number **IP0417**

Inotersen

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for inotersen (**Tegsedi®**) injection for subcutaneous use.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Inotersen (Tegsedi) is considered medically necessary when the following are met:

1. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Individual meets **ALL** of the following criteria:
    A. Age 18 years or older
    B. Documented diagnosis of hereditary transthyretin-mediated (hATTR) amyloidosis confirmed by a transthyretin (TTR) genetic variant (pathogenic or likely pathogenic variant)
    C. Documentation of symptomatic polyneuropathy confirmed by history and clinical exam, electromyography, or nerve conduction velocity testing (Examples of polyneuropathy symptoms

include reduced motor strength/coordination and impaired sensation (e.g., pain, temperature, vibration, touch).

D. Documentation that other causes of neuropathy have been excluded (for example, diabetes)
E. No prior liver transplant
F. The medication is prescribed by, or in consultation with, a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis

Dosing. 284 mg subcutaneously once weekly

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of inotersen (Tegsedi) is considered medically necessary when the above medical necessity criteria are met AND there is documentation of beneficial response (for example, improvement in neuropathy symptoms, stabilization of or slowed disease progression, improvement in quality of life).

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Wainua (eplontersen subcutaneous injection), 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 hATTR with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

2. **Treatment of Cardiomyopathy hATTR in the Absence of Polyneuropathy Symptoms.**
   There is no data evaluating the safety and efficacy of inotersen or patisiran for treatment of cardiomyopathy hATTR in the absence of polyneuropathy symptoms. Clinical trials with inotersen and patisiran only included individuals with hATTR amyloidosis and polyneuropathy symptoms.

3. **Treatment of Polyneuropathy Not Related to hATTR Amyloidosis.**
   There is no data evaluating the safety and efficacy of inotersen or patisiran for the treatment of neuropathy from non-hATTR etiologies. Clinical trials with inotersen and patisiran only included individuals with hATTR amyloidosis and polyneuropathy symptoms.

Background

OVERVIEW
Tegsedi, an antisense oligonucleotide, is indicated for treatment of adults with **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)**.[1] Tegsedi has not been studied in patients with a history of liver transplantation. hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines
A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Tegsedi for polyneuropathy of hATTR.[5] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi are recommended for patients with hATTR polyneuropathy.

For patients with hATTR with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax/Vyndaqel are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

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).

References

1. Tegsedi® injection [prescribing information]. Waltham, MA: Sobi/Akcea; June 2022.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
5. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC*. 2023;81(11):1076-1126.