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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Neuromuscular Drugs	**Original Policy Date:**	October 26, 2018
Subject:	Tegsedi	**Page:**	1 of 7

Last Review Date: December 8, 2023

Tegsedi

Description

Tegsedi (inotersen)

Background
Tegsedi (inotersen) is an antisense oligonucleotide that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues (1).

Regulatory Status
FDA-approved indication: Tegsedi is a transthyretin-directed antisense oligonucleotide indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults (1).

Tegsedi has a boxed warning for thrombocytopenia. Tegsedi can cause reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. Tegsedi should not be initiated in patients with a platelet count below 100 x 10^9/L. Patients who are not able to adhere to the recommended laboratory monitoring or to the related treatment recommendations should not receive Tegsedi (1).

Tegsedi also has a boxed warning for glomerulonephritis. Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. Tegsedi-treated patients who develop glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations. Tegsedi should generally not be initiated in patients with a urine protein to creatinine ratio (UPCR) of 1000 mg/g or greater, or eGFR below 45 mL/minute/1.73 m^2. If acute glomerulonephritis is confirmed, Tegsedi should be

permanently discontinued. Serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, and UPCR should be monitored every 2 weeks during treatment with Tegsedi (1).

Tegsedi is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tegsedi REMS Program, because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis (1).

Other warnings for Tegsedi include: stroke and cervicocephalic arterial dissection; inflammatory and immune effects; liver effects; hypersensitivity reactions/antibody formation; uninterpretable platelet counts; and reduced serum vitamin A levels.

Various scales are used to capture the disease burden and progression of polyneuropathy in hATTR amyloidosis. The extent of disability is typically captured by the Familial Amyloidotic Polyneuropathy (FAP) staging system and/or the polyneuropathy disability (PND) scoring system. Neuropathy Impairment Score (NIS) can be used to quantify impairment and progression of neuromuscular conditions at time of diagnosis and during treatment (2). Tegsedi clinical trials included only Stage 1 and 2 FAP patients with a NIS score ≥ 10 and ≤130 (3).

The safety and effectiveness of Tegsedi in pediatric patients have not been established (1).

Related policies
Amvuttra, Onpattro

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Tegsedi may be considered **medically necessary** if the conditions indicated below are met.

Tegsedi may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age and older

Diagnosis

Patient must have the following:

Polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis

AND ALL of the following:

1. Diagnosis of hATTR confirmed by genetic testing **OR** tissue biopsy showing amyloid deposition
2. Patient must have **ONE** of the following baseline scores:
    a. Polyneuropathy disability (PND) score ≤ IIIb (see Appendix 1)
    b. FAP Stage 1 or 2 (see Appendix 2)
3. Platelet count ≥ 100 x 10^9/L (100,000 cells/µL)
4. eGFR ≥ 45 mL/minute/1.73 m^2
5. Prescriber agrees to monitor the following during therapy:
    a. Platelet count
    b. Renal function (serum creatinine, eGFR, and urinalysis)
    c. Liver function (ALT, AST, and total bilirubin)
6. Patient and prescriber are both enrolled in the Tegsedi REMS Program
7. Prescriber agrees to supplement the patient with the recommended daily allowance of Vitamin A if indicated
8. Patient has **NONE** of the following:
    a. New York Heart Association (NYHA) class III or IV heart failure
    b. Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.)
    c. Prior liver transplantation
9. Prescribed by or in consultation with a neurologist, or a specialist in the treatment of the patient's diagnosis
10. **NO** dual therapy with another Prior Authorization (PA) medication for polyneuropathy caused by hATTR amyloidosis (see Appendix 3)

Prior – Approval *Renewal* Requirements

Age 18 years of age and older

Diagnosis

Patient must have the following:

Polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis

AND ALL of the following:

1. Patient condition has improved or stabilized
2. Platelet count ≥ 100 x 10^9/L (100,000 cells/µL)
3. eGFR ≥ 45 mL/minute/1.73 m^2

4. Prescriber agrees to monitor the following during therapy:
    a. Platelet count
    b. Renal function (serum creatinine, eGFR, and urinalysis)
    c. Liver function (ALT, AST, and total bilirubin)
5. Patient and prescriber are both enrolled in the Tegsedi REMS Program
6. Prescriber agrees to supplement the patient with the recommended daily allowance of Vitamin A if indicated
7. **NO** dual therapy with another Prior Authorization (PA) medication for polyneuropathy caused by hATTR amyloidosis (see Appendix 3)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 12 prefilled syringes per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Tegsedi (inotersen) is an antisense oligonucleotide used to treat polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR). Tegsedi contains boxed warnings for thrombocytopenia and glomerulonephritis. Tegsedi is available only through the Tegsedi REMS program. The safety and effectiveness of Tegsedi in pediatric patients have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Tegsedi while maintaining optimal therapeutic outcomes.

References

1. Tegsedi [package insert]. Waltham, MA: Sobi, Inc.; June 2022.

2. Dyck, P. James., González-Duarte, A., Obici, L., Polydefkis, M., Wiesman, J., Antonino, I., Litchy, W, Dyck, Peter J. (2019, August 08). Development of measures of polyneuropathy impairment in hATTR amyloidosis: From NIS to mNIS+7. Accessed on September 04, 2020. Available at: https://www.sciencedirect.com/science/article/pii/S0022510X19303569
3. ClinicalTrials.gov [online]. NIH U.S. National Library of Medicine. 2000. A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy. Accessed on September 4, 2020. Available at: https://clinicaltrials.gov/ProvidedDocs/98/NCT01737398/Prot_000.pdf

Policy History

Date	Action
October 2018	Addition to PA
November 2018	Annual review. Addition of Vitamin A supplementation requirement per SME
May 2019	Addition of renewal requirement: Patient has been assessed for improvement and has experienced a clinical benefit from therapy
June 2019	Annual review
September 2019	Annual review
September 2020	Annual review and reference update. Addition of requirements per FEP: pathogenic TTR mutation confirmed by genetic testing and one of the following baseline scores: PND score ≤ IIIb, FAP Stage 1 or 2 and NIS ≥10 and ≤130.
December 2021	Annual editorial review and reference update
July 2022	Addition of Appendix 3 and modification of dual therapy requirement to no dual therapy with a PA medication for hATTR amyloidosis; to align with BCBS association criteria addition of: revised initiation criteria to include OR tissue biopsy showing amyloid deposition; 9.Patient has NONE of the following: a.New York Heart Association (NYHA) class III or IV heart failure b. Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.) c. Prior liver transplantation, revised continuation to include improvement or stabilization of condition
September 2022	Annual review
December 2023	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.

Appendix 1 - Polyneuropathy Disability (PND) Severity Scoring System

Polyneuropathy Disability (PND) Score	
Stage 0	No impairment
Stage I	Sensory disturbances but preserved walking capability
Stage II	Impaired walking capability but ability to walk without a stick or crutches
Stage IIIA	Walking only with the help of one stick or crutches
Stage IIIB	Walking only with the help of two sticks or crutches
Stage IV	Confined to a wheelchair or bedridden

Appendix 2 - FAP Stage Severity Scoring System

FAP Stage	
Stage 0	No symptoms
Stage I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
Stage II	Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
Stage III	Wheelchair bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

Appendix 3 - List of PA Medications for Polyneuropathy caused by hATTR Amyloidosis

Generic Name	Brand Name
inotersen	Tegsedi
patisiran	Onpattro
vutrisiran	Amvuttra