In patients with polyneuropathy of hereditary ATTR amyloidosis

TREAT EARLY AND TARGET THE SOURCE WITH TEGSEDI™[1]

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

Abbreviation: ATTR, transthyretin-mediated amyloidosis.

INDICATION

TEGSEDI is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults.

WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

See full Prescribing Information for complete boxed WARNING.

Thrombocytopenia

- **TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening**
- **Testing prior to treatment and monitoring during treatment is required**

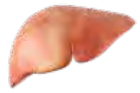
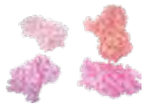
Glomerulonephritis

- **TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure**
- **Testing prior to treatment and monitoring during treatment is required**

TEGSEDI is available only through a restricted distribution program called the TEGSEDI Risk Evaluation and Mitigation Strategy (REMS) Program.

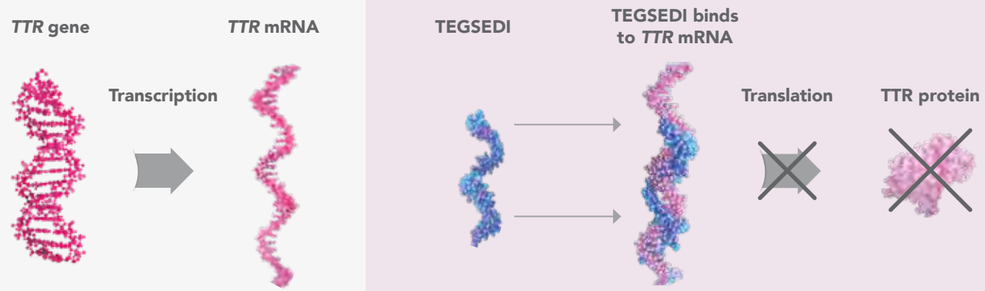
Please see additional Important Safety Information on back cover and accompanying full Prescribing Information for TEGSEDI, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis.

IN PATIENTS WITH POLYNEUROPATHY OF HEREDITARY ATTR AMYLOIDOSIS, **TEGSEDI™ TARGETS THE DISEASE AT ITS SOURCE[1-3]**

LIVER	TTR TETRAMER	TTR MONOMER	MISFOLDED TTR PROTEINS	AMYLOID FIBRILS
				
The TTR protein is primarily synthesized by the liver	TTR proteins are excreted from the liver as tetramers	Tetramers dissociate into monomers due to *TTR* gene mutations	Monomers can misfold and aggregate into fibrils	Amyloid fibrils can deposit in various organs and cause systemic dysfunction

TEGSEDI binds to and causes degradation of *TTR* mRNA, inhibiting TTR protein synthesis[1]

TEGSEDI MECHANISM OF ACTION[1]



TEGSEDI prevents the synthesis of TTR protein in the liver through degradation of *TTR* mRNA[1]

HEREDITARY ATTR AMYLOIDOSIS WITH POLYNEUROPATHY IS AN UNDER-RECOGNIZED, DEBILITATING, AND PROGRESSIVE DISEASE[2,4-6]

- Hereditary ATTR amyloidosis with polyneuropathy is an autosomal dominant, systemic disease[7]
- Patients with hereditary ATTR amyloidosis experience a median onset of signs or symptoms several decades earlier than those with wild-type ATTR amyloidosis (39.0 [25.9-64.5] to 53.9 years vs 71.4 [60.1-81.6] years).[2,7]

Misdiagnosis is common, with 45% to 57% of patients with hereditary ATTR amyloidosis being initially misdiagnosed.[8,9]

The average time to a correct diagnosis is 2 to 4 years.[8,10]

IDENTIFY THE RIGHT PATIENT FOR TREATMENT WITH TEGSEDI

Manifestations of polyneuropathy

- Signs and symptoms can include sensory, motor, and autonomic neuropathy which can progress rapidly[4]
- FAP staging and PND scoring can assess patients' neuropathic impairment at time of treatment initiation[11]

Genetic confirmation of hereditary ATTR amyloidosis

- Diagnosis can include assessment of clinical symptoms and evidence of amyloid deposition, and ultimately requires a genetic test[5,12]
- ICD-10-CM code for hereditary ATTR amyloidosis is E85.1

Genetic testing can confirm a diagnosis of hereditary ATTR amyloidosis early to optimize management[5,12]

Abbreviations: FAP, familial amyloid polyneuropathy; PND, polyneuropathy disability.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Thrombocytopenia

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IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

- Platelet count below 100 x 10^9/L
- History of acute glomerulonephritis caused by TEGSEDI
- History of a hypersensitivity reaction to TEGSEDI

TEGSEDI is available only 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.

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Tegsedi™ (inotersen) injection 284 mg/1.5 mL

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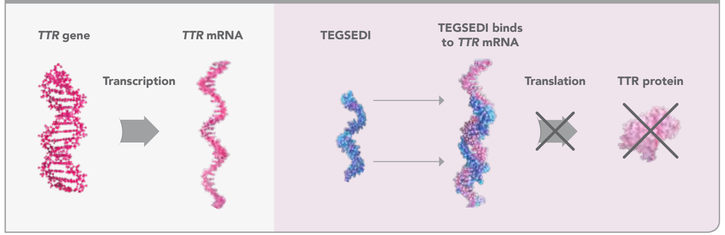

TEGSEDI prevents the synthesis of TTR protein in the liver through degradation of *TTR* mRNA[1]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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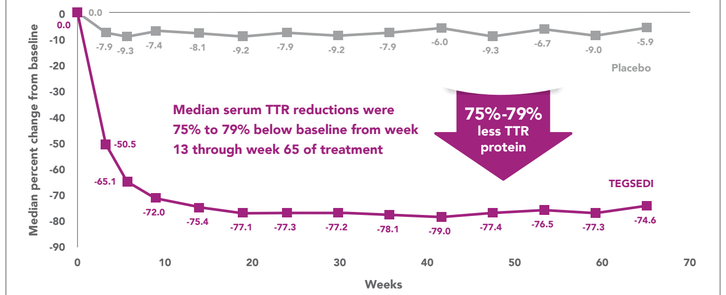
IN THE NEURO-TTR STUDY, **TEGSEDI DELIVERED POWERFUL TTR KNOCKDOWN[1,2]**

Initiation of TEGSEDI therapy substantially reduced TTR protein levels and sustained reductions through week 65 of treatment[1]

Similar TTR reductions were observed regardless of *TTR* mutation, sex, age, or race[1]

MEDIAN PERCENT CHANGE FROM BASELINE IN SERUM TTR OVER TIME[1,13]



In patients with polyneuropathy of hereditary ATTR amyloidosis, TEGSEDI powerfully knocks down circulating TTR protein levels and reduces formation of TTR amyloid fibril deposits[1,2]

TEGSEDI was studied in a robust pivotal study and open-label extension in adults with polyneuropathy of hereditary ATTR amyloidosis[2,14]

- The study included 173 adult patients (ages 18-82) with stage 1 or 2 polyneuropathy of hereditary ATTR amyloidosis and Neuropathy Impairment Score of 10-130[2]
- Coprimary end points included the modified Neuropathy Impairment Score +7 (mNIS+7) and Norfolk Quality of Life-Diabetic Neuropathy total score (QoL-DN) at week 66[1]
- Patients treated with TEGSEDI achieved a 19.7-point improvement in mNIS+7 and an 11.7-point improvement in Norfolk QoL-DN at 66 weeks vs patients receiving placebo (P<0.001 for each, respectively)[1,2]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Thrombocytopenia (cont'd)

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (eg, petechiae, easy bruising, hematoma, subconjunctival bleeding, gingival bleeding, epistaxis, hemoptysis, irregular or heavier than normal menstrual bleeding, hematemesis, hematuria, hematochezia, melena), neck stiffness, or atypical severe headache. Patients and caregivers should be instructed to be vigilant for symptoms of thrombocytopenia and seek immediate medical help if they have concerns.

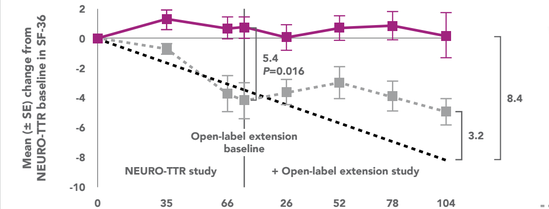
97% (135/139) of patients who completed NEURO-TTR elected to continue on to the open-label extension study[2]

- At the conclusion of the study, patients were given the opportunity to enroll in an open-label extension study and continue on treatment with TEGSEDI or switch from placebo—patients were studied for up to 5 years of treatment with TEGSEDI[14]
- Enrollment in the open-label extension was limited only to those patients who met inclusion criteria, completed NEURO-TTR, and elected to enroll in the open-label extension[15]
- The open-label extension was not a placebo-controlled study and all patients in the open-label extension were aware they were on active drug[14]

TERTIARY END POINT OF NEURO-TTR
AS SHOWN BY SF-36, TEGSEDI HALTED WORSENING OF HEALTH-RELATED QOL COMPARED WITH PLACEBO[14,a]

SF-36 is a non–disease-specific measure of health-related QoL[14]

CHANGE FROM BASELINE IN SF-36 SCORE[14,b,c]



Abbreviations: QoL, quality of life; SF-36, Short-Form 36 Health Survey.
[a]Placebo refers to actual placebo during NEURO-TTR and projected placebo for the open-label extension study.
[b]The pivotal study and open-label extension study used SF-36v2.[14]
[c]A greater value indicates a greater quality of life.[14]
[d]Trend line of NEURO-TTR placebo data points, with calculated slope extrapolated beyond placebo data collection.

Early treatment of the polyneuropathy of hereditary ATTR amyloidosis is critical in preventing further decline in patients' neuropathy and QoL[2,6,15]

IMPORTANT SAFETY INFORMATION
ADVERSE REACTIONS

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than in those on placebo were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%).

Please see additional Important Safety Information on back cover and accompanying full Prescribing Information for TEGSEDI, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis.

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

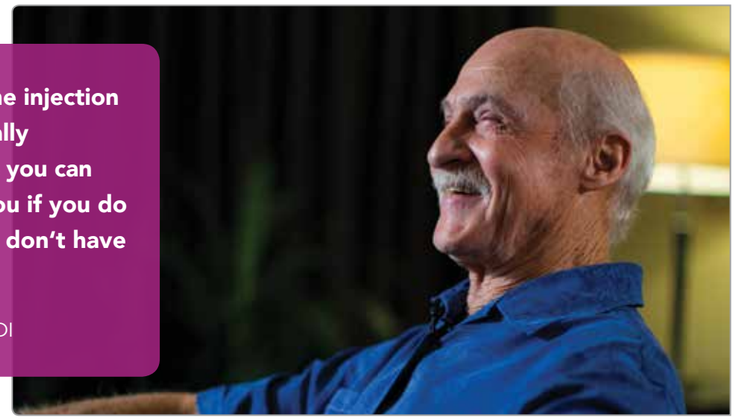
TEGSEDI™ IS THE FIRST AND ONLY SELF-ADMINISTERED, SUBCUTANEOUS TREATMENT FOR THE POLYNEUROPATHY OF HEREDITARY ATTR AMYLOIDOSIS IN ADULTS[1]

TEGSEDI is available in a single-dose, prefilled syringe with a safety spring (284 mg/1.5 mL solution; 27-gauge, 8-mm needle), providing patients with a once-weekly subcutaneous injection[1]

- The recommended dosage of TEGSEDI is 284 mg injected subcutaneously once weekly[1]
- For consistency of dosing, patients should be instructed to give the injection on the same day every week[1]
  - If a dose is missed, patients should be instructed to take the missed dose as soon as possible, unless the next scheduled dose is within 2 days. In this situation, the patient should be directed to skip the missed dose and take the next scheduled dose on the scheduled day[1]
- TEGSEDI should be refrigerated, but can be stored for up to 6 weeks at room temperature[1]

As part of AKCEA CONNECT®, the patient support program, your patients can contact a Nurse Case Manager for proactive, ongoing support, injection training, and education

Help your patients and their caregivers connect to personalized one-on-one support with AKCEA CONNECT—visit **AkceaConnect.com**.



> **“Doing a simple, at-home injection once per week was really practical. It also means you can typically take it with you if you do some traveling, so you don’t have to miss a shot.”**
>
> **Mike** | Patient taking TEGSEDI

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Glomerulonephritis and Renal Toxicity

TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1, glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. Follow recommended monitoring and treatment recommendations for renal parameters. TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or greater. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.

Please see accompanying full Prescribing Information for TEGSEDI, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis.

THE FIRST AND ONLY SELF-ADMINISTERED, SUBCUTANEOUS TREATMENT FOR THE POLYNEUROPATHY OF HEREDITARY ATTR AMYLOIDOSIS IN ADULTS[1]

THE POWER OF TTR KNOCKDOWN

- TEGSEDI targets the disease at its source, powerfully knocking down circulating TTR protein levels and reducing formation of TTR amyloid fibril deposits[1,2]
- TEGSEDI delivered significant, sustained improvements compared with placebo in measures of both neuropathy and QoL[1]

THE INDEPENDENCE OF SUBCUTANEOUS SELF-ADMINISTRATION

- With TEGSEDI, patients have the independence to self-administer at a time and place that works for them[1]

THE CONFIDENCE OF ROUTINE MONITORING

- Due to the risk of thrombocytopenia and glomerulonephritis, TEGSEDI is only available through a REMS[1]
- Regular monitoring for your patients can be confidently delivered through the TEGSEDI safety program[1]
- AKCEA CONNECT is here as your partner to provide support and reliable resources patients can trust

BUSINESS CARD

IMPORTANT SAFETY INFORMATION
DRUG INTERACTIONS

Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (including nonprescription products that affect platelets) or anticoagulants concomitantly with TEGSEDI. Because of the risk of glomerulonephritis and renal toxicity, caution should be used when using nephrotoxic drugs and other drugs that may impair renal function concomitantly with TEGSEDI.

References: **1.** TEGSEDI [package insert]. Boston, MA: Akcea Therapeutics, Inc; 2018. **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. doi:10.1056/NEJMoa1716793. **3.** Ueda M, Ando Y. Recent advances in transthyretin amyloidosis therapy. *Transl Neurodegener*. 2014;3:19. doi:10.1186/2047-9158-3-19. **4.** Conceição I, González-Duarte A, Obici L, et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9. doi:10.1111/jns.12153. **5.** Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31. doi:10.1186/1750-1172-8-31. **6.** Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care*. 2017;23(suppl 7):S107-S112. **7.** Coelho T, Maurer MS, Suhr OB. THAOS—the Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin*. 2013;29(1):63-76. doi:10.1185/03007995.2012.754348. **8.** Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis). Amyloidosis Support Groups website. http://amyloidosissupport.org/support_groups/fam_isabell_attr.pdf. Accessed May 16, 2019. **9.** Lousada I, Maurer M, Warner M, Guthrie S, Hsu K, Grogan M. Amyloidosis research consortium cardiac amyloidosis survey: results from patients with ATTR amyloidosis and their caregivers [abstract]. *Orphanet J Rare Dis*. 2017;12(suppl 1):P7. **10.** Plante-Bordeneuve V, Ferreira A, Lalu T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology*. 2007;69(7):693-698. **11.** Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord*. 2013;6(2):129-139. doi:10.1177/1756285612470192. **12.** Adams D, Suhr OB, Hund E, et al; from European Network for TTR-FAP (ATTReuNET). First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29(suppl 1):S14-S26. doi:10.1097/WCO.0000000000000289. **13.** Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis [supplemental appendix]. *N Engl J Med*. 2018;379(1):1-36. doi:10.1056/NEJMoa1716793. **14.** Data on file. Akcea Therapeutics, Inc. **15.** Brannagan T, Wang AK, Coelho T, et al. Open-label extension of NEURO-TTR study in patients with hereditary transthyretin (hATTR) amyloidosis: long-term update. Poster presented at: 2018 Peripheral Nerve Society (PNS) Annual Meeting; July 22-25, 2018; Baltimore, MD.

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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WARNINGS AND PRECAUTIONS

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Stroke and Cervicocephalic Arterial Dissection

TEGSEDI may cause stroke and cervicocephalic arterial dissection. In clinical studies, 1 of 161 (0.6%) TEGSEDI-treated patients experienced carotid artery dissection and stroke. Educate patients on the symptoms of stroke and central nervous system arterial dissection. Instruct patients to seek help as soon as possible if symptoms of stroke or arterial dissection occur.

Inflammatory and Immune Effects

Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including TEGSEDI. In clinical studies, serious inflammatory and immune adverse reactions occurred in TEGSEDI-treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)–positive systemic vasculitis.

Liver Effects

In clinical studies, 8% of TEGSEDI-treated patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN) compared with 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN compared with no patients on placebo. Monitor ALT, aspartate aminotransferase, and total bilirubin at baseline and every 4 months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.

Hypersensitivity Reactions/Antibody Formation

TEGSEDI can cause hypersensitivity reactions. In clinical studies, 6 of 161 (4%) TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. These reactions generally occurred within 2 hours of administration of TEGSEDI. Antibodies to TEGSEDI were present when the reactions occurred. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reactions to TEGSEDI.

Uninterpretable Platelet Counts: Reaction Between Antiplatelet Antibodies and Ethylenediaminetetraacetic acid (EDTA)

In Study 1, 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping compared with 13% of patients on placebo. If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (eg, sodium citrate, heparin) in the blood collection tube. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

Reduced Serum Vitamin A Levels and Recommended Supplementation

TEGSEDI treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking TEGSEDI. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (eg, night blindness).

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AKCEA® THERAPEUTICS