



+



**WITH EVERY NEW PATIENT**

## CHECKLIST FOR NEW PATIENTS STARTING TEGSEDI™

Patient name: \_\_\_\_\_

Contact information: \_\_\_\_\_

Your patient is almost ready to start treatment with TEGSEDI. Once you have completed the following tasks, be sure to return all completed forms to AKCEA CONNECT™.

- Encourage your patient to enroll in AKCEA CONNECT by completing the enclosed **AKCEA CONNECT Patient Enrollment and Authorization Form**.
- Complete the enclosed **TEGSEDI Prescription Start Form**.
- Complete the **Quest Lab Monitoring Requisition Form** provided via mail by Quest Diagnostics.
- Help your patient enroll in TEGSEDI REMS.
  - Review the TEGSEDI REMS Patient Guide with your patient
  - Complete the **TEGSEDI REMS Patient Enrollment Form** with your patient and provide him or her with a copy of the signed form
  - Provide your patient with a TEGSEDI REMS Wallet Card
- Use the enclosed sample template to customize a **Letter of Medical Necessity for TEGSEDI** with your patient's information.
- Scan and email all completed forms to AKCEA CONNECT at [akceaconnect@akceatx.com](mailto:akceaconnect@akceatx.com) or complete the enclosed Fax Form 2 and send it with all completed forms to 1-866-252-3239.

**A representative from AKCEA CONNECT will be in touch shortly after you have submitted all completed forms.**

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

  
**Tegsedi™**  
(inotersen) injection  
284 mg/1.5 mL

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

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

### WARNINGS AND PRECAUTIONS

#### Thrombocytopenia

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1, platelet counts below  $100 \times 10^9/L$  occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below  $75 \times 10^9/L$  occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. One patient in a clinical trial experienced a fatal intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below  $100 \times 10^9/L$ . Follow recommended monitoring and treatment recommendations for platelet count.

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.

#### 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.

**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.**

#### 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).

### 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%).

### 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.

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

# Patient Enrollment and Authorization Form



Phone: 1-866- AKCEATX (1-866-252-3289) Fax: 1-866-AKCEAFX (1-866-252-3239)  
Email: AkceaConnect@akceatx.com

Patient Support and Experience Services is available to provide essential support, regardless of the management plan you and your physician choose.

Patient Support and Experience Services is a complimentary program offered by Akcea Therapeutics that is staffed by nurse case managers, who are registered nurses with clinical knowledge and funding expertise.

Patient Support and Experience nurse case managers provide ongoing support in the following areas:

- **Coverage issues and funding options:** Assisting patients with insurance coverage questions and research funding options
- **Education:** Collaborating with your healthcare team to answer questions and provide educational materials related to your disease
- **Management support:** Assisting with solutions for balancing all aspects of disease management when faced with major life challenges

In order to participate in the patient support program (PSP) and receive these patient services, PSP needs to receive, use, and share your personal health information. In this Form, we are asking you to agree to let your healthcare providers, health plan, or health insurers release your health information (sometimes called "Protected Health Information" or "PHI") to PSP and to allow PSP and its agents to use and share your PHI.

The PHI we need includes medical records regarding your medical condition and treatment, information about how well you are able to manage your treatment plan, information about your insurance coverage and benefits, and identifying information about you (including your name, address, date of birth, and Social Security number). PSP will only use this PHI in the ways described in this Form or as otherwise permitted by law.

**You do not have to sign this Form and, if you choose not to sign it, your ability to obtain treatment from your healthcare providers and your eligibility for benefits under your health plan will not be affected. However, if you do not sign this Form, PSP may not be able to provide you with the services listed above.**

To enroll in the PSP program for personalized support, please read the information on the back page and fill out, sign, and date the Form. Please read this Form carefully and contact PSP if you have any questions.

## PATIENT INFORMATION

First Name: \_\_\_\_\_ Last Name: \_\_\_\_\_

Date of Birth: \_\_\_\_/\_\_\_\_/\_\_\_\_ Gender: \_\_\_\_\_ Last four digits of SS#: XXX-XX-XXXX \_\_\_\_\_

Street Address: \_\_\_\_\_ City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

Telephone Number(s) of Patient (or Designated Representative, if applicable): \_\_\_\_\_

Email of Patient (or Designated Representative) (optional): \_\_\_\_\_

### Designated Representative (Please fill out this section ONLY if the person signing this Authorization is not the Patient)

Name of Person Authorizing Release: \_\_\_\_\_ Relationship to Patient: \_\_\_\_\_

### Additional Permissions (optional)

Name: \_\_\_\_\_ Relationship to Patient: \_\_\_\_\_

Telephone: \_\_\_\_\_ Cell Phone: \_\_\_\_\_ Email: \_\_\_\_\_

## Authorization to Receive Patient Services and Communications

I (or my representative) authorize Akcea Therapeutics, including, but not limited to, its affiliates, business partners, employees, sub-contractors, agents, and other representatives (together, "Akcea") to provide me with patient support services related to any of Akcea's products including, but not limited to, online support, financial assistance services, compliance and persistency services, and other therapy support services, as well as any Information or materials related to such services.

**I (or my representative) agree and acknowledge that any Akcea personnel providing such support services are not employed by my healthcare professional, nor are providing medical treatment or advice.**

### Authorization to Use and Disclose Protected Health Information

I (or my representative) agree to permit the Authorized Parties listed below to disclose my Protected Health Information ("PHI") to Akcea Therapeutics, for the uses described below.

### The Authorized Parties include:

1. My primary care physician, evaluating and/or treating physician, and any specialist or other healthcare providers involved in my treatment ("Providers");
2. The distributor, pharmacy, or home health agency that dispenses my medical therapy ("Distributors"); or (3) my health insurer, payer, or patient assistance program ("Payers") and (4) Laboratory.

The PHI that may be disclosed includes medical reports, orders, prescriptions and records, histories, findings, prognoses, plans of care and discharge summaries, billing information, insurance claims, utilization review reports and laboratory testing results.

The **Authorized Parties** may disclose my PHI to Akcea, so that Akcea may use and disclose the PHI for the following purposes:

1. **Coordination of care:** Between me, the Providers, Distributors, or Payers for the coordination of my medical care, including therapy adherence reminders.
2. **Disease management/patient education:** To provide information, training and case management services to me (or my representative), and any Providers, Payers, and Distributors.
3. **Clinical research/treatment protocols:** To inform me (or my representative) of clinical research studies, treatment protocols, or disease-related surveys that may benefit me.
4. **Reviewing insurance benefits/plan and/or funding options:** To review, co-verify, and to assist me (or my representative) in understanding the benefits provided by my Payer, to verify what services my benefits cover and help me obtain the services ordered by my Provider, to coordinate benefits, to determine appeal requirements, and to identify other sources of payment, if necessary.
5. **Billing and payment:** To coordinate the preparation, filing, and processing of health insurance claims, the evaluation of coding (billing) issues, and assist with the resolution of any claims issues relating to my therapy.
6. **Distribution of therapy:** To coordinate the distribution of medical therapy to me.

7. **Product orders:** To fulfill any product orders and answer any questions that I (or my representative) may provide to the Akcea case management team, and otherwise to inform me (or my representative) about other services that may be of interest to me (or my representative).

8. **Government agencies:** To provide information as required or requested by representatives of government agencies, review boards, and others who watch over the safety of drugs (or operations) of pharmaceutical manufacturers.

9. **Other uses of PHI:** To de-identify the information about me and to use this de-identified information in performing patient and community education, clinical protocol development, marketing studies, or for other commercial purposes as determined by Akcea.

10. **Contact:** To contact me (or my representative) by mail, email, fax, telephone call, text message (including calls and text messages made with an automatic telephone dialing system), and other mutually agreed-upon means.

## Notice

I (or my representative) understand that once my PHI has been disclosed to Akcea, federal privacy laws may no longer protect it from further disclosure.

However, Akcea agrees to protect my PHI by using and disclosing it only for the purposes described in this Authorization or as permitted by law. **I understand that I do not have to sign this Authorization and that if I do not sign this Authorization, or choose to revoke it, my ability to obtain medical care and/or therapy, or my eligibility or enrollment for insurance benefits will not be affected. However, if I do not sign this Authorization, Akcea may not be able to provide the services described above.**

## Signature

I (or my representative) have read and understand the terms of this Authorization Form. This Authorization shall be in effect for 10 years from the date of my signature, or the date of last enrollment, whichever comes first, unless a shorter period is required by law. I (or my representative) may revoke this Authorization at any time by sending a written letter which includes my name and address, to Akcea Therapeutics at the address or fax on the top of this form. I (or my representative) have the right to receive a copy of this Authorization upon request. I understand that my healthcare providers, insurers, and health plans may receive remuneration (payment) from Akcea in exchange for disclosing My Health Information to Akcea.

**Signature of Patient or Designee:**

X \_\_\_\_\_

**Date:** \_\_\_\_\_

Fax completed form to 1-866-AKCEAFX (1-866-252-3239) or

Email completed form to AkceaConnect@akceatx.com

# Prescription Start Form

Phone: 1-866- AKCEATX (1-866-252-3289) Fax: 1-866-AKCEAFX (1-866-252-3239)

Email: AkceaConnect@akceatx.com



**All fields mandatory**

## 1. PATIENT INFORMATION

First Name	Middle Initial	Last Name	Date of Birth (mm/dd/yyyy)	Gender <input type="checkbox"/> M <input type="checkbox"/> F
Home Address			City	
State	Zip Code	Last four digits of SS#	XXX-XX-	
Shipping Address (If Not Home Address)				
Care of (If different than Pt.)		City	State	Zip Code
Home Phone # <input type="checkbox"/> OK to leave Message		Mobile # <input type="checkbox"/> OK to Text	Best Time to Call	Preferred Language (If other than English)
Email Address		Pt. Representative/ Caregiver Name		
Relationship	Pt. Rep Phone #	Pt. Rep Email Address		

## 2. INSURANCE INFORMATION: (Please include front and back copies of insurance cards) If no insurance please check here

Primary Insurance	Policy Holder	Date of Birth (mm/dd/yyyy)
Policy #	Group #	Phone #
Secondary Insurance	Policy Holder	Date of Birth (mm/dd/yyyy)
Policy #	Group #	Phone #
Prescription Insurance	Policy Holder	Date of Birth (mm/dd/yyyy)
Member ID #	Group #	Rx Bin #
		PCN #
		Phone #

## 3. HEALTHCARE PROVIDER (HCP) INFORMATION

HCP First Name	HCP Last Name	Office/Clinic/ Facility Name		
National Provider ID (NPI) #	Tax ID #	State License #	Phone #	
Address				
City		State	Zip Code	
Office Contact		Contact Phone #	Office Fax #	
Email Address		Preferred Method of Contact		

## 4. PRESCRIPTION INFORMATION: TEGSEDI™ 284 MG/1.5 ML NDC# 72126-007-01 PREFILLED SYRINGE

**Primary Diagnosis:**  Hereditary Transthyretin Amyloidosis (hATTR) ICD-10: E85.1  Other Diagnosis/Code \_\_\_\_\_

NKDA Allergies \_\_\_\_\_

Concurrent Medications \_\_\_\_\_

**Nurse Injection Training:** Authorize RN visit to provide education related to therapy, disease state, administration and dosing, and titration per prescriber order

Inject 284 mg/1.5 mL subcutaneously  Once weekly  Other Quantity: \_\_\_\_\_  
(Maximum 30 day supply)

**IMPORTANT: TEGSEDI REMS Patient Attestation form required every 90 days to continue therapy.** Refills \_\_\_\_\_

Prescriber Signature (Dispense as Written) **X** \_\_\_\_\_ Date \_\_\_\_\_

Prescriber Signature (Substitution Allowed) **X** \_\_\_\_\_ Date \_\_\_\_\_

Supervising Physician Signature (where required) **X** \_\_\_\_\_ Date \_\_\_\_\_

**Prescriber signature required for consent and to validate prescriptions. Prescriber attests that this is his/her signature. NO STAMPS.**

**The prescriber is to comply with his/her state specific prescription requirements such as e-prescribing, state specific prescription form, fax language, etc. Non-compliance with state specific requirements could result in outreach to the prescriber.**

*AKCEA CONNECT™ is committed to partnering with patients and HCPs to ensure safety and proper injection technique. Learning and using proper injection technique is crucial for patients taking TEGSEDI. AKCEA CONNECT will provide up to three sessions of injection training by a nurse and a sharps container for enrolled patients. Patients covered by government plans may not qualify for this program.*

### 5. LABORATORY TESTING AND MEDICAL HISTORY

TEGSEDI™ should not be initiated in patients with a platelet count < 100 x 10<sup>9</sup>/L and a UPCR ≥ 1000 mg/g.

Platelets ≥ 100 x 10<sup>9</sup>/L    Y     N     Date drawn \_\_\_\_\_    UPCR < 1000 mg/g    Y     N     Date drawn \_\_\_\_\_  
 eGFR \_\_\_\_\_    Date drawn \_\_\_\_\_    Serum creatinine \_\_\_\_\_    Date drawn \_\_\_\_\_  
 ALT \_\_\_\_\_    Date drawn \_\_\_\_\_    AST \_\_\_\_\_    Date drawn \_\_\_\_\_  
 Total bilirubin \_\_\_\_\_    Date drawn \_\_\_\_\_    Urinalysis \_\_\_\_\_    Date drawn \_\_\_\_\_

**History of:**

Polyneuropathy                      Y     N     (ICD-10: G63)  
 Bil. Carpal Tunnel Syndrome      Y     N     (ICD-10: G56.03)  
 Cardiomyopathy                      Y     N     (ICD-10: I43)  
 Syncope                                Y     N     (ICD-10: R55)  
 Cardiac Arrhythmia                  Y     N     (ICD-10: I49.9)  
 Congestive Heart Failure          Y     N     (ICD-10: I50.9)  
 Transplant History                  Y     N     (ICD-10: Z94)  
 Transplant Type: \_\_\_\_\_

Diarrhea                                Y     N     (ICD-10: K59.1)  
 Constipation                         Y     N     (ICD-10: K59.00)  
 Unexplained Weight Loss          Y     N     (ICD-10: R63.4)  
 Renal Nephropathy                  Y     N     (ICD-10: N29)  
 Vitreous opacities                  Y     N   
 Autonomic Dysfunctions            Y     N   
 Ambulatory Status:  
 Unassisted     Cane     Walker     Wheelchair

### 6. CURRENT AND HISTORICAL MEDICATIONS

Diflunisal        Current?    Y     N     Duration of therapy \_\_\_\_\_    Other  \_\_\_\_\_  
 Tafamidis        Current?    Y     N     Duration of therapy \_\_\_\_\_  
 Patisiran        Current?    Y     N     Duration of therapy \_\_\_\_\_

### 7. CONSENT, AND STATEMENT OF MEDICAL NECESSITY: HCP SIGNATURE REQUIRED

I certify that TEGSEDI is medically necessary for this patient and that I have reviewed this therapy with the patient and will be monitoring the patient's treatment. I verify that the patient and the healthcare provider information on the prescription start form was completed by me or at my direction and that the information contained herein is complete and accurate to the best of my knowledge. I understand that I must comply with my practicing state's specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc. Non-compliance with state-specific requirements could result in outreach to me by the dispensing pharmacy.

I authorize dispensing pharmacies, e.g., Accredo and other designated operators of the AKCEA CONNECT Program to perform a preliminary assessment of benefit verification for this patient and furnish information requested by the patient's insurer that is available on this form. I understand that insurance verification is ultimately the responsibility of the provider and third-party reimbursement is affected by a variety of factors. While Accredo tries to provide accurate information, they and Akcea make no representations or warranties as to the accuracy of the information provided.

I authorize AKCEA CONNECT Program its affiliates, agents, and contractors (collectively, Akcea) to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy designated by the patient utilizing their benefit plan.

**CLINICIAN SIGNATURE: REQUIRED FOR DOCUMENTATION**

I verify that the patient and the healthcare provider information on this prescription start form was completed by me or at my direction and that the information contained herein is complete and accurate to the best of my knowledge. I certify that my patient has agreed in writing to be contacted by AKCEA CONNECT Program or dispensing pharmacy, e.g., Accredo and be furnished with Program or other information or materials.

Prescriber Authorization Signature  \_\_\_\_\_ Date \_\_\_\_\_

Please see full Prescribing Information for TEGSEDI, including boxed WARNING regarding the risk of thrombocytopenia and glomerulonephritis, at TEGSEDIhcp.com. Patients should alert Accredo with any changes in status or insurance.

## What is TEGSEDI?

TEGSEDI is a medicine used to treat the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. It is not known if TEGSEDI is safe and effective in children.

### **Risks of Serious Bleeding, Kidney Inflammation, and Kidney Failure**

TEGSEDI can cause serious side effects such as serious bleeding caused by a low platelet count (thrombocytopenia) and kidney inflammation (called glomerulonephritis) and kidney failure. Please talk about these side effects with your doctor.

You must get blood tests to check your platelet count, as well as blood and urine tests to check your kidneys, to take TEGSEDI.

#### **Low Platelet Counts:**

TEGSEDI may cause the number of platelets in your blood to be reduced. This is a common side effect of TEGSEDI. When your platelet count is too low, your body cannot form clots. You could have serious bleeding that could lead to death. You need to call your doctor right away or go to the emergency room.

The signs and symptoms of low platelet count may include:

- Unusual bruising or a rash of tiny reddish-purple spots, often on the lower legs
- Bleeding from skin cuts that does not stop or oozes
- Bleeding from your gums or nose
- Blood in urine or stools
- Bleeding into the whites of your eyes
- Sudden severe headaches or neck stiffness
- Vomiting blood or coughing up blood
- Abnormal or heavy periods (menstrual periods)

#### **Kidney Inflammation (Glomerulonephritis) and Kidney Failure:**

Your kidneys may stop working properly. Glomerulonephritis can lead to kidney damage and kidney failure that needs dialysis. You need to call your doctor right away or go to the emergency room.

The signs and symptoms of kidney inflammation include:

- Puffiness or swelling in your face, feet, or hands
- New onset or worsening shortness of breath and coughing
- Blood in your urine or brown urine
- Foamy urine (proteinuria)
- Passing less urine than usual

**If you have 1 or more of the symptoms for the serious side effects of low platelet count, kidney inflammation, or kidney failure, call your doctor right away or go to the emergency room.**

**Do not take TEGSEDI unless your doctor confirms that it is safe to continue TEGSEDI treatment.**

## TEGSEDI™ REMS Patient Guide

### What is the TEGSEDI REMS?

Because of the risks associated with TEGSEDI, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS). As part of the REMS, your doctor will discuss the risks of TEGSEDI with you and give you materials to review on your own.

Both you and your doctor must sign the *Patient Enrollment Form* for you to receive TEGSEDI. Your doctor will provide a copy of the signed form to the TEGSEDI REMS.

The TEGSEDI REMS also requires TEGSEDI to be dispensed by a REMS-certified pharmacy. Your doctor will send your prescription to the certified pharmacy, who will contact you if they need more information. The pharmacy will only dispense a 1-month supply of TEGSEDI to you at a time.

### What Do I Need To Do?

#### **Before Starting Treatment:**

Tell your doctor if you take blood thinners or medicines that affect blood clotting.

Your doctor will test your blood and urine to check your platelet count and kidney function before you start TEGSEDI.

#### **During Treatment:**

Your doctor will do blood and urine tests to check your platelet count and kidney function every 1-2 weeks or more frequently if he/she thinks you need it.

Watch for symptoms of low platelet count, kidney inflammation, or kidney failure and call your doctor if you have concerns.

Carry your *TEGSEDI Wallet Card* with you at all times. The *Wallet Card* tells other doctors that you are taking TEGSEDI. In the event of an emergency, give the *Wallet Card* to the emergency room doctor and inform all of your healthcare providers about this treatment.

#### **If You Stop Treatment:**

If your doctor has you stop taking TEGSEDI, you will need to continue to get your blood and urine tested for 8 more weeks.

### Where can I find more information about the TEGSEDI REMS?

If you have questions about the REMS, you can call the TEGSEDI REMS Coordinating Center at 1-844-483-4736, 8:00 AM-8:00 PM EST.

Phone: 1-844-483-4736 | [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) | Fax: 1-855-483-4736



## TEGSEDI™ REMS Patient Enrollment Form

TEGSEDI is available only through the TEGSEDI REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive TEGSEDI. Your certified healthcare provider will help you complete this form and provide you with a copy.

**Prescribers and patients:** Please complete this form online at [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) or, once completed, fax it to the REMS at 1-855-483-4736.

*\*Indicates required field*

PATIENT INFORMATION				
First Name*:	Last Name*:	MI:	Gender: <input type="checkbox"/> M <input type="checkbox"/> F	Date of Birth (Month/Day/Year)*:
Email:				
Address Line 1*:				
Address Line 2:				
City*:	State*:	Zip Code*:	Phone Number*:	
Preferred method(s) of contact: <input type="checkbox"/> Phone <input type="checkbox"/> Email				

PRESCRIBER INFORMATION		
First Name*:	Last Name*:	
Practice/Facility Name:		
Address Line 1:		
Address Line 2:		
City:	State:	Zip Code:
Email:		
Phone Number*:	DEA:	NPI*:

**Healthcare provider: Provide a copy of this form to the patient.**

Phone: 1-844-483-4736 | [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) | Fax: 1-855-483-4736





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US-TEG-1800138 10/18

## TEGSEDI™ PATIENT WALLET CARD

Carry this card with you at all times. **SHOW THIS CARD** if you go to the emergency room or see any healthcare provider.

Tell any healthcare provider that sees you that you are being treated with **TEGSEDI**.

**Prescriber's name (first & last):**

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**Prescriber phone #:**

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## Patient information

TEGSEDI may cause side effects that are severe or life threatening.

Call your doctor or go to the emergency room **RIGHT AWAY** if you have any of these symptoms:

- Unusual bruising or a rash of tiny reddish-purple spots, often on the lower legs
- Bleeding from skin cuts that does not stop or oozes
- Bleeding from your gums or nose
- Blood in urine or stools
- Bleeding into the whites of your eyes
- Sudden severe headaches or neck stiffness
- Vomiting blood or coughing up blood
- Abnormal or heavy menstrual periods
- Puffiness or swelling in your face, feet, or hands
- New onset or worsening shortness of breath and coughing
- Blood in your urine or brown urine
- Foamy urine (proteinuria)
- Passing less urine than usual

## Important information for healthcare providers

This patient is receiving TEGSEDI for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

TEGSEDI has a risk of serious bleeding with severe thrombocytopenia and a risk of glomerulonephritis. Patients treated with TEGSEDI are being regularly monitored for these risks via the following lab results: platelets, estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR).

## Sample Letter of Medical Necessity

The sample letter of medical necessity should be customized by your office and submitted to insurers as part of the prior authorization or predetermination process. If you would like more information on how to utilize this template letter, please call Akcea Connect™ toll-free at 1-866-252-3289, Monday through Friday, 8 AM to 8 PM (ET).

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[Practice Letterhead]

[Date]

[Name of Medical Director] [Title]

[Name of Insurer]

[Address of Insurer]

[City, State, ZIP code]

Re: [Patient's Name]

[Patient ID Number]

[Diagnosis code(s) and description(s)]

I am writing to provide additional information regarding the medical necessity of treating one of your members, **[Patient Name]**, with TEGSEDI™ (inotersen) injection for subcutaneous, self-administered use. TEGSEDI was approved by the FDA on October 5, 2018 for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults.<sup>i</sup> This letter provides information about my patient's medical history, and my rationale for use of TEGSEDI.

### Disease Overview

Hereditary transthyretin amyloidosis (hATTR) is a rare, systemic, and life-threatening disease.<sup>ii iii</sup> The hereditary version of ATTR (hATTR) impacts multiple organ systems resulting in a range of complications that impair quality of life.<sup>iv v vi</sup> Over 120 mutational variants of the *TTR* gene have been identified and are expressed in an autosomal dominant manner with variable penetrance.<sup>vii viii</sup> Hereditary ATTR amyloidosis is associated with a point mutation in the *TTR* gene, and ATTR presents with substantial clinical heterogeneity. Nonspecific symptoms and manifestations overlap with other disorders resulting in delayed differential diagnosis.<sup>ix x</sup> In addition, given the array of symptoms, many patients see multiple physicians and specialists prior to ATTR confirmation through tissue biopsy analysis and/or genetic testing.<sup>xi xii</sup>

### Patient's Diagnosis and History

The history and course of hATTR-PN for **[Patient Name]** are as follows:

Diagnosis of hATTR with E85.1 (Neuropathic hereditary amyloidosis):

**[Insert comment / information regarding the date and method of diagnosis:**

- **MUST include comment on genetic confirmation of pathogenic mutation for hATTR**
- **MAY include evidence of amyloid by tissue biopsy of salivary gland, subcutaneous fatty tissue of the abdominal wall or sural nerve, immunohistochemistry/mass spectrometry results, scintigraph (technetium-99m stannous pyrophosphate [PYP] scanning)**
- **SHOULD include clinical manifestations (e.g., past/present working diagnosis prior to hATTR confirmation such as polyneuropathy, nephropathy, ocular manifestations, bilateral carpal tunnel syndrome (CTS), lumbar spinal canal stenosis, etc.)**

Signs, Symptoms, Scoring / Staging of Polyneuropathy:

**Clinical signs and symptoms of disease progression**

## Sample Letter of Medical Necessity

- **MUST include baseline Polyneuropathy Disability (PND) score and/or Familial Amyloidosis Polyneuropathy (FAP) stage**
- **MUST include clinical evidence of peripheral and/or autonomic neuropathy (e.g. symmetrical length-dependent peripheral neuropathy, orthostatic hypotension, sexual dysfunction, uncontrolled diarrhea, alternating diarrhea/constipation, etc.)**
- **SHOULD include impact on quality of life, activities of daily living, or impact upon the caregiver**
- **SHOULD include comment on patient hospitalizations, and/or frequency of office visits**

Previous treatments: **[Insert comment / information on current therapy and previous treatments identified to manage or slow the progression of the disease (e.g. diflunisal) and resulting symptoms, including but not limited to those related to CTS, spinal canal stenosis, GI symptoms, ocular manifestations, neuropathy, and renal failure.]**

Despite the use of a variety of treatments and therapies to treat the symptoms of hATTR-PN described in this letter, my patient continues to decline in daily function and quality of life is significantly impacted by hATTR-PN. It is my opinion that TEGSEDI injection is the appropriate therapeutic treatment for my patient. TEGSEDI prevents the synthesis of the TTR protein in the liver through degradation of the TTR mRNA.<sup>xiii</sup> In clinical trials, initiation of TEGSEDI therapy substantially reduced TTR protein levels and sustained reductions through 65 weeks.<sup>xiv</sup> TEGSEDI has a manageable safety profile.<sup>xv</sup>

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,<sup>xvi</sup> and is available only through a restricted distribution program under a REMS due to the risk of thrombocytopenia and glomerulonephritis.<sup>xvii</sup> Regular monitoring for patients can be confidently delivered through the TEGSEDI safety program,<sup>xviii</sup> and patients have the ability to self-administer at a time and place that works for them.<sup>xix</sup>

### Treatment Description and Rationale

TEGSEDI is a transthyretin-directed antisense oligonucleotide (ASO) indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.<sup>xx</sup> In clinical trials, TEGSEDI delivered significant, sustained improvements in measures of both neuropathy and quality of life.<sup>xxi</sup> The efficacy of TEGSEDI was demonstrated in a robust, randomized, double-blind, placebo-controlled, multicenter clinical trial in adults with polyneuropathy caused by hATTR.<sup>xxii</sup> Patients were randomized in a 2:1 ratio to receive either TEGSEDI (n=113) or placebo (n=60), respectively, as a subcutaneous injection administered once per week for 65 weeks.<sup>xxiii</sup> The coprimary efficacy end points were the change from baseline to week 66 in the modified Neuropathy Impairment Score +7 (mNIS+7) and Norfolk Quality of Life–Diabetic Neuropathy (QoL-DN) scores.<sup>xxiv</sup>

TEGSEDI significantly improved measures of neuropathic progression vs placebo.<sup>xxv</sup> Patients treated with TEGSEDI achieved a 19.7-point benefit at 66 weeks vs patients receiving placebo ( $P<0.001$ )—approximately 10 times the clinically meaningful threshold.<sup>xxvi</sup> More than one-third of patients treated with TEGSEDI saw improvements in neuropathy at 66 weeks (36% vs 19.2% on placebo,  $P=0.033$ ).<sup>xxvii</sup>

TEGSEDI significantly improved quality of life vs placebo.<sup>xxviii</sup> Patients treated with TEGSEDI achieved a clinically meaningful 11.7-point benefit on Norfolk QoL-DN at 66 weeks vs patients receiving placebo ( $P<0.001$ )—approximately 12 times the clinically meaningful threshold.<sup>xxix</sup> Half of patients treated with TEGSEDI saw improvements in quality of life at 66 weeks (50% vs 26.9% on placebo,  $P=0.08$ ).<sup>xxx</sup> Patients treated with TEGSEDI experienced similar improvements regardless age, sex, race, region, Neuropathy Impairment Score, Val30Met mutation status, and disease stage.<sup>xxxi</sup>

Given the seriousness of my patient's condition, and the sustained improvements in measures of both neuropathy and quality of life<sup>xxxii</sup> as described by the TEGSEDI clinical trials, it is my professional medical opinion that **[Patient Name]** should receive treatment with TEGSEDI.

## Sample Letter of Medical Necessity

I certify that both the patient and the healthcare provider understand the requirements of, and are in compliance with, the parameters of the TEGSEDI REMS program.

Print Name: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_

I trust that this information is helpful to you in understanding why I have prescribed treatment with TEGSEDI. If you require any additional information, please do not hesitate to contact me at [(XXX) XXX-XXXX].

Sincerely,

**[Physician's name]**, MD

Title

Address

City, State, ZIP

Phone

Email

Enclosures: **[Clinic notes, Prescribing Information, FDA approval letter, other supportive medical literature]**

Please see **Important Safety Information (ISI)** at: [www.TegsediHCP.com](http://www.TegsediHCP.com)

Please see **Risk Evaluation and Mitigation Strategy** at <https://www.tegsedirems.com/>

- Please note that laboratory tests must be measured prior to treatment, continue to be monitored weekly after treatment initiation, and for 8 weeks following discontinuation of treatment, as directed
- Please note that TEGSEDI is only available through a restricted distribution program called the TEGSEDI REMS.

Please see **TEGSEDI (inotersen)** full Prescribing Information here: <https://tegsedihcp.com/wp-content/uploads/2018/10/prescribing-information.pdf>

More information on **TEGSEDI** can be found here: [www.TegsediHCP.com](http://www.TegsediHCP.com)

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<sup>i</sup> USPI p1/¶4/L1

<sup>ii</sup> Adams D, Amitay O, Coelho T. Patients *with* hereditary ATTR amyloidosis experience *an* increasing burden of illness as the disease progresses. *Orphanet J Rare Dis.* 2015;10(suppl 1):P58.

<sup>iii</sup> 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.

<sup>iv</sup> Coelho T, et al. *Curr Med Res Opin.* 2013;29(1):63-76.

<sup>v</sup> Suhr O, et al. *J Int Med.* 1994;235(5):479-85.

<sup>vi</sup> Hawkins PN, et al. *Ann Med.* 2015;47(8):625-38.

<sup>vii</sup> Rowczenio DM, et al. *Hum Mutat.* 2014;35(9):E2403-12.

<sup>viii</sup> Hou X, Aguilar MI, Small DH. *FEBS J.* 2007;274(7):1637-50.

## Sample Letter of Medical Necessity

- 
- ix Lousada I, et al. Orphanet J Rare Dis. 2017;12(suppl 1):165.
- x Lousada I, et al. Presented at: the First European Congress on Hereditary ATTR Amyloidosis. November 2015; Paris, France
- xi Lousada I, et al. Orphanet J Rare Dis. 2017;12(suppl 1):165.
- xii Lousada I, et al. Presented at: the First European Congress on Hereditary ATTR Amyloidosis. November 2015; Paris, France
- xiii USPI p17/Section12.1/¶1; Benson p23/c1/¶3/L1-4
- xiv USPI p17/Section12.2/¶2
- xv USPI p8/Section 5
- xvi USPI p4/Section2.1/¶1/Section2.2/bullet2/p23/section16/¶1; DOF (needle dimensions on file at Akcea); DOF/TEGSEDI IFU p1/Guide to Parts)
- xvii USPI p7/Section5.3/¶1/L1-3
- xviii USPI p4/Section2.3/p5/Section2.4
- xix USPI p4/Section2.1/¶1/L1,¶2/L3-4/p4/Section 2.2
- xx USPI p1/¶4/L1
- xxi Tegsedi™ Full Prescribing Information, p.20
- xxii USPI p19 Section14/¶1/L1-2
- xxiii USPI p19 Section14/¶1/L3-6
- xxiv USPI p19 Section14/¶2/L1-3
- xxv USPI p19/Section14/Table 3
- xxvi USPI p19/Section14.2/Table 3; Benson NEJM 2018 p24/c1/¶2/L9-12
- xxvii Benson 2018 p25/c2/¶2/8-13/Table S5 Supplemental Index
- xxviii USPI p19/Section14/Table 3
- xxix USPI p19/Section14.2/Table 3; DOF/TEGSEDI Brand Blueprint append, TEGSEDI Clinical Profile p28
- xxx Benson 2018 p25/c2/¶2/8-13/Table S5 Supplemental Index
- xxxi USPI p24/¶1
- xxxii USPI p19/Section14 ¶3/L1-2, ¶4/L1-2, ¶5, Table 3/ p19 Section14/¶Last Paragraph/L1-4; Benson NEJM 2018 p25/c1/¶4,c2/¶3/L1-8



Phone: 1-866- AKCEATX (1-866-252-3289) Fax: 1-866-AKCEAFX (1-866-252-3239) Email: AkceaConnect@akceatx.com

DATE: \_\_\_\_\_

**TO:**

**FROM:**

NAME: **AKCEA CONNECT™**

NAME: \_\_\_\_\_

ATTN: \_\_\_\_\_

ADDRESS: \_\_\_\_\_

SUBJECT: \_\_\_\_\_

STATE: \_\_\_\_\_ ZIP: \_\_\_\_\_

PHONE: \_\_\_\_\_

FAX: \_\_\_\_\_

EMAIL: \_\_\_\_\_

COMMENTS: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

NUMBER OF PAGES INCLUDED: \_\_\_\_\_

**ALL OF THE FOLLOWING COMPLETED FORMS ARE INCLUDED:**

- AKCEA CONNECT Patient Enrollment and Authorization Form
- TEGSEDI™ Prescription Start Form
- QUEST Lab Monitoring Requisition Form
- TEGSEDI REMS Patient Enrollment Form
- Letter of Medical Necessity for TEGSEDI



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**MEDICATION GUIDE**  
**TEGSEDI (Teg-SED-ee)**  
**(inotersen)**

**injection, for subcutaneous use**

**What is the most important information I should know about TEGSEDI?**

**TEGSEDI can cause serious side effects, including:**

- **low platelet counts (thrombocytopenia).** TEGSEDI may cause the number of platelets in your blood to be reduced. This is a common side effect of TEGSEDI. When your platelet count is too low, your body cannot form clots. You could have serious bleeding that could lead to death. **Call your healthcare provider immediately if you have:**
  - unusual bruising or a rash of tiny reddish-purple spots, often on the lower legs
  - bleeding from skin cuts that does not stop or oozes
  - bleeding from your gums or nose
  - blood in your urine or stools
  - bleeding into the whites of your eyes
  - sudden severe headaches or neck stiffness
  - vomiting or coughing up blood
  - abnormal or heavy periods (menstrual bleeding)
- **kidney inflammation (glomerulonephritis).** Your kidneys may stop working properly. Glomerulonephritis can lead to severe kidney damage and kidney failure that needs dialysis. **Call your healthcare provider immediately if you have:**
  - puffiness or swelling in your face, feet or hands
  - new onset or worsening shortness of breath and coughing
  - blood in your urine or brown urine
  - foamy urine (proteinuria)
  - passed less urine than usual

Your healthcare provider will do laboratory tests to check your platelet count and kidneys before you start TEGSEDI and while you are using it. Your healthcare provider should also do laboratory tests for 8 weeks after you stop TEGSEDI. **It is important that you make sure you get these laboratory tests done.**

- **Because of the risk of serious bleeding caused by low platelet counts and because of the risk of kidney problems, TEGSEDI is available only through a restricted program called the TEGSEDI Risk Evaluation and Mitigation (REMS) Program.**
  - Before you begin using TEGSEDI, you must enroll in the TEGSEDI REMS Program. Talk to your healthcare provider about how to enroll in the TEGSEDI REMS Program.
  - **You must agree to get your laboratory testing done while you are in the TEGSEDI REMS Program.**
  - You can only get TEGSEDI from a certified pharmacy that participates in the TEGSEDI REMS Program. Your healthcare provider can give you information on how to find a certified pharmacy.
  - For more information, including a list of certified pharmacies go to [www.TEGSEDIREMS.com](http://www.TEGSEDIREMS.com) or call 1-844-483-4736.

**What is TEGSEDI?**

TEGSEDI is a medicine used to treat the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. It is not known if TEGSEDI is safe and effective in children.

**Do not use TEGSEDI if you have:**

- a platelet count that is low.
- had kidney inflammation (glomerulonephritis) caused by TEGSEDI.
- had an allergic reaction to inotersen or any of the ingredients in TEGSEDI. See the end of this Medication Guide for a complete list of ingredients in TEGSEDI.

**Before you start using TEGSEDI, tell your healthcare provider about all your medical conditions, including if you:**

- have or had bleeding problems.
- have or had kidney problems.
- are pregnant or plan to become pregnant. It is not known if TEGSEDI can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TEGSEDI can pass into your breast milk or harm your baby. Talk with your healthcare provider about the best way to feed your baby while you are using TEGSEDI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**Especially tell your healthcare provider if you take:**

- Vitamin A or beta-carotene supplements. Your healthcare provider should tell you to take vitamin A, but only take the amount they tell you to take.
- blood thinners (anticoagulants) or medicines that affect blood clotting.

Ask your healthcare provider or pharmacist if you are not sure if you take any of these medicines. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

### How should I use TEGSEDI?

- Read the detailed **Instructions for Use** that come with your TEGSEDI.
- Your healthcare provider will show you or your caregiver how to inject TEGSEDI the first time.
- If you or your caregiver have any questions, ask your healthcare provider.
- TEGSEDI is injected under your skin (subcutaneously) in your stomach area (abdomen), or the front of your upper legs (thighs) by you or a caregiver. A caregiver may also give you an injection of TEGSEDI in the outer area of your upper arm.
- **Do not** inject into the same site each time.
- **Do not** inject into the 2-inch area around the belly-button (naval).
- **Do not** inject where the skin is bruised, tender, red, or hard.
- **Do not** inject into areas with scars or tattoos.
- **Do not** inject through clothing.
- Follow your healthcare provider's instructions on when to inject TEGSEDI.
- TEGSEDI should be injected 1 time each week on the same day.
- If you miss a dose, take the missed dose as soon as possible, unless your next scheduled dose is within 2 days. If your next scheduled dose is within 2 days, skip the missed dose and take your next scheduled dose on the scheduled day.

### What are possible side effects of TEGSEDI?

#### TEGSEDI may cause serious side effects, including:

- See "**What is the most important information I should know about TEGSEDI?**"
- **stroke.** TEGSEDI may cause a stroke. One person taking TEGSEDI had a stroke, which occurred within 2 days after the first dose. Signs or symptoms of stroke may include:
  - sudden numbness or weakness especially on one side of the body
  - severe headache or neck pain
  - confusion
  - problems with vision, speech, or balance
  - droopy eyelids

#### Get emergency help immediately if you have symptoms of stroke.

- **inflammatory and immune system problems.** Some people taking TEGSEDI had serious inflammatory and immune system problems. Symptoms of inflammatory and immune system problems included unexpected change in walking, weakness and spasms in legs, back pain, weight loss, headache, vomiting, and problems with speech.
- **liver effects.** TEGSEDI may cause liver problems. Your healthcare provider should do laboratory tests to check your liver before you start TEGSEDI and while you are using it. Tell your healthcare provider if you have symptoms that your liver may not be working right, which could include unexpected nausea and vomiting, stomach pain, being not hungry, yellowing of the skin, or having dark urine.
- **allergic reactions.** TEGSEDI may cause serious allergic reactions. These allergic reactions often occur within 2 hours after injecting TEGSEDI. Get emergency help immediately if you have any symptoms of an allergic reaction including:

○ joint pain	○ chest pain	○ high blood pressure
○ chills	○ flushing	○ difficulty swallowing
○ redness on palms of hands	○ tremor or jerking movements	
○ muscle pain	○ flu-like symptoms	

- **eye problems (low vitamin A levels).** Treatment with TEGSEDI will lower the Vitamin A levels in your blood. Your healthcare provider should tell you to take Vitamin A supplements while using TEGSEDI. Your healthcare provider will tell you how much to take. Call your healthcare provider if you get eye problems, such as having difficulty seeing at night or in low lit areas (night blindness). Your healthcare provider should send you to see an eye doctor (ophthalmologist).

**The most common side effects of TEGSEDI include:** injection site reactions (such as redness or pain at the injection site), nausea, headache, tiredness, low platelet counts (thrombocytopenia), and fever.

These are not all the possible side effects of TEGSEDI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store TEGSEDI?**

- Store TEGSEDI in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original container.
- **Do not** freeze.
- TEGSEDI prefilled syringes can also be kept at room temperature that is no higher than 86°F (30°C) in the original container for up to 6 weeks.
- **Do not** let TEGSEDI reach temperatures above 86°F (30°C).
- If you do not use TEGSEDI kept at room temperature within 6 weeks, throw it away.
- Protect from light.

**Keep TEGSEDI and all medicines out of the reach of children.**

**General information about the safe and effective use of TEGSEDI**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TEGSEDI for a condition for which it has not been prescribed. Do not give TEGSEDI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TEGSEDI that was written for health professionals.

**What are the ingredients in TEGSEDI? Active ingredients:** inotersen

**Inactive ingredients:** purified water (water for injection), hydrochloric acid and or sodium hydroxide for pH adjustment

Distributed by Akcea Therapeutics, Inc, Boston, MA

TEGSEDI is registered in the US Patent and Trademark Office© 2017

For more information about TEGSEDI, contact Akcea Therapeutics, Inc., at 1-844-483-4763 or go to [www.TEGSEDIREMS.com](http://www.TEGSEDIREMS.com).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 10/2018

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TEGSEDI™ safely and effectively. See full prescribing information for TEGSEDI.

TEGSEDI (inotersen) injection, for subcutaneous use  
Initial U.S. Approval: 10/2018

### 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. (5.1)
- Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.1)

#### Glomerulonephritis

- TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. (5.2)
- Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.2)

TEGSEDI is available only through a restricted distribution program called the TEGSEDI REMS Program (5.3).

## INDICATIONS AND USAGE

TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults (1).

## DOSAGE AND ADMINISTRATION

- The recommended dosage is 284 mg administered by subcutaneous injection once weekly. (2.1)
- Laboratory tests must be measured prior to treatment, continue to be monitored after treatment initiation, and for 8 weeks following discontinuation of treatment, as directed. (2.3, 2.4)

## DOSAGE FORMS AND STRENGTHS

Injection: 284 mg/ 1.5 mL in a single-dose prefilled syringe (3)

## CONTRAINDICATIONS

- Platelet count less than  $100 \times 10^9/L$  (4, 5.1)
- History of acute glomerulonephritis caused by TEGSEDI (4, 5.2)
- Patients with a history of a hypersensitivity reaction to TEGSEDI (4, 5.7)

## WARNINGS AND PRECAUTIONS

- *Stroke and Cervicocephalic Arterial Dissection:* These adverse events occurred within 2 days of first dose and with symptoms of cytokine release. Educate patients on symptoms of stroke and central nervous system arterial dissection. (5.4)
- *Inflammatory and Immune Effects:* Serious neurologic adverse reactions consistent with inflammatory and immune effects occurred. (5.5)
- *Liver Effects:* Monitor alanine amino transferase, aspartate aminotransferase, and total bilirubin every 4 months during treatment and in case of symptoms of hepatic dysfunction. (5.6)
- *Hypersensitivity Reactions:* If these occur, discontinue and initiate appropriate therapy. (5.7)
- *Uninterpretable Platelet Counts: Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid:* Platelet clumping can cause uninterpretable platelet measurement; repeat test if this is suspected. (5.8)
- *Reduced Serum Vitamin A Levels and Recommended Supplementation:* Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. (5.9)

## ADVERSE REACTIONS

The most common adverse reactions (those that occurred in at least 20% of TEGSEDI-treated patients and more frequently than on placebo) were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals, Inc. at 1-833-642-5232 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: THROMBOCYTOPENIA and GLOMERULONEPHRITIS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

##### 2.1 Dosing Information

##### 2.2 Administration

##### 2.3 Assessment Prior to Initiating TEGSEDI

##### 2.4 Laboratory Testing and Monitoring after Initiating TEGSEDI

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Thrombocytopenia

##### 5.2 Glomerulonephritis and Renal Toxicity

##### 5.3 TEGSEDI REMS Program

##### 5.4 Stroke and Cervicocephalic Arterial Dissection

##### 5.5 Inflammatory and Immune Effects

##### 5.6 Liver Effects

##### 5.7 Hypersensitivity Reactions/Antibody Formation

##### 5.8 Uninterpretable Platelet Counts: Reactions between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid (EDTA)

##### 5.9 Reduced Serum Vitamin A Levels and Supplementation

#### 6 ADVERSE REACTIONS

##### 6.1 Clinical Trials Experience

##### 6.2 Immunogenicity

- 7 **DRUG INTERACTIONS**
  - 8 **USE IN SPECIFIC POPULATIONS**
    - 8.1 Pregnancy
    - 8.2 Lactation
    - 8.4 Pediatric Use
    - 8.5 Geriatric Use
    - 8.6 Renal Impairment
    - 8.7 Hepatic Impairment
  - 11 **DESCRIPTION**
  - 12 **CLINICAL PHARMACOLOGY**
    - 12.1 Mechanism of Action
    - 12.2 Pharmacodynamics
    - 12.3 Pharmacokinetics
  - 13 **NONCLINICAL TOXICOLOGY**
    - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  - 14 **CLINICAL STUDIES**
  - 16 **HOW SUPPLIED/STORAGE AND HANDLING**
  - 17 **PATIENT COUNSELING INFORMATION**
- \*Sections or subsections omitted from the full prescribing information are not listed.**
-

## FULL PRESCRIBING INFORMATION

### WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

#### **Thrombocytopenia**

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial patient died from intracranial hemorrhage.

TEGSEDI is contraindicated in patients with a platelet count below  $100 \times 10^9/L$  [*see Contraindications (4) and Warnings and Precautions (5.2)*].

Prior to starting TEGSEDI, obtain a platelet count [*see Dosage and Administration (2.3)*]. During treatment, monitor platelet counts weekly if values are  $75 \times 10^9/L$  or greater, and more frequently if values are less than  $75 \times 10^9/L$  [*see Dosage and Administration (2.4) and Warnings and Precautions (5.1)*].

If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional [*see Warnings and Precautions (5.1)*].

Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than  $100 \times 10^9/L$ , to verify that platelet counts remain above  $75 \times 10^9/L$  [*see Dosage and Administration (2.4)*].

#### **Glomerulonephritis**

TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial patient who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis-dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection [*see Warnings and Precautions (5.2)*].

TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher [*see Dosage and Administration (2.4) and Warnings and Precautions (5.2)*].

Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis [*see Dosage and Administration (2.3)*]. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every every two weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below  $45 \text{ mL/minute}/1.73 \text{ m}^2$ , pending further evaluation of the cause.

If a dose is held, once eGFR increases to  $\geq 45$  mL/minute/1.73 m<sup>2</sup>, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.2)*].

### **TEGSEDI REMS Program**

Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program [see *Warnings and Precautions (5.3)*].

## **1 INDICATIONS AND USAGE**

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

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Dosing Information**

The recommended dose of TEGSEDI is 284 mg injected subcutaneously once weekly.

For consistency of dosing, patients should be instructed to give the injection on the same day every week.

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.

### **2.2 Administration**

- TEGSEDI is intended for subcutaneous use only.
- The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified healthcare professional. Patients and/or caregivers should be trained in the subcutaneous administration of TEGSEDI in accordance with the Instructions for Use.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit [see *How Supplied/Storage and Handling (16)*].
- Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. It is important to rotate sites for injection.
  - If injected in the upper arm, the injection should be administered by a person other than the patient.

- Injection should be avoided at the waistline and other sites where pressure or rubbing from clothing may occur.
- TEGSEDI should not be injected into areas of skin disease or injury.
- Tattoos and scars should also be avoided.
- TEGSEDI prefilled syringe should be allowed to reach room temperature prior to injection.
  - Remove from refrigerated storage at least 30 minutes prior to use.
  - Other warming methods should not be used.
- Use each prefilled syringe only once.

### **2.3 Assessment Prior to Initiating TEGSEDI**

Measure platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, and perform urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation [*see Dosage and Administration (2.4) and Warnings and Precautions (5.1 and 5.2)*].

### **2.4 Laboratory Testing and Monitoring to Assess Safety after Initiating TEGSEDI**

Monitor platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin during treatment with TEGSEDI, and for 8 weeks following discontinuation of treatment.

#### Platelet Count

Do not initiate TEGSEDI in patients with a platelet count less than  $100 \times 10^9/L$ .

Recommendations for platelet monitoring frequency and TEGSEDI dosing are specified in [Table 1](#). If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible, and hold dosing until platelet count is confirmed. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable (e.g., clumped sample) [*see Warnings and Precautions (5.8)*].

**Table 1: TEGSEDI Monitoring and Treatment Recommendations for Platelet Count**

Platelet count (x10 <sup>9</sup> /L)	Monitoring Frequency	Dosing
At least 100	Weekly	Continue to dose weekly.
At least 75 to less than 100	Weekly	Stop treatment. Do not restart unless platelet count is greater than 100.
At least 50 to less than 75	Twice weekly until 3 successive values above 75; then weekly monitoring.	Stop treatment. Do not restart TEGSEDI in patients with thrombocytopenia, unless there have been 3 successive values above 100 and the benefit of TEGSEDI outweighs the risk of thrombocytopenia and potential bleeding.
At least 25 to less than 50*	Twice weekly until 3 successive values above 75; then weekly monitoring.  Consider more frequent monitoring if additional risk factors for bleeding are present.#	Stop treatment. Do not restart TEGSEDI in patients with thrombocytopenia, unless there have been 3 successive values above 100 and the benefit of TEGSEDI outweighs the risk of thrombocytopenia and potential bleeding.  Corticosteroids recommended.  Consider discontinuation of any antiplatelet agents or anticoagulants.
Less than 25**†	Daily until 2 successive values above 25. Then monitor twice weekly until 3 successive values above 75. Then weekly monitoring until stable.	Stop TEGSEDI.  Corticosteroids recommended.  Consider discontinuation of any antiplatelet agents or anticoagulants.

\* It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receive glucocorticoid therapy to reverse the platelet decline [see *Warnings and Precautions (5.1)*].

# Additional risk factors for bleeding include age >60 years, receiving anticoagulant or antiplatelet medicinal products, or prior history of major bleeding events.

†Patients who discontinue therapy with TEGSEDI because of platelet counts below 25 x10<sup>9</sup>/L should not reinitiate therapy.

## Renal Monitoring

TEGSEDI should generally not be initiated in patients with a urine protein to creatinine ratio (UPCR) of 1000 mg/g or higher. Monitor serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, and UPCR every 2 weeks during treatment with TEGSEDI. Hold TEGSEDI in patients who develop a UPCR of 1000 mg/g or higher, or estimated glomerular filtration rate (eGFR) below 45 mL/minute/1.73 m<sup>2</sup>, pending further evaluation of the cause.

If a dose is held, once eGFR increases to  $\geq 45$  mL/minute/1.73 m<sup>2</sup>, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In the case of UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.

## Liver Tests

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin every four months during treatment with TEGSEDI.

## **3 DOSAGE FORMS AND STRENGTHS**

Injection: 284 mg/1.5 mL clear, colorless to pale yellow solution in a single-dose prefilled syringe.

## **4 CONTRAINDICATIONS**

TEGSEDI is contraindicated in patients with:

- Platelet count below  $100 \times 10^9/L$  [*see Warnings and Precautions (5.1)*]
- History of acute glomerulonephritis caused by TEGSEDI [*see Warnings and Precautions (5.2)*]
- History of a hypersensitivity reaction to TEGSEDI [*see Warnings and Precautions (5.7)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Thrombocytopenia**

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1 [*see Clinical studies (14)*], platelet counts below  $100 \times 10^9/L$  occurred in 25% of TEGSEDI-treated patients, compared with 2% of patients on placebo. Platelet counts below  $75 \times 10^9/L$  occurred in 14% of TEGSEDI-treated patients, compared to no patient on placebo. In Study 1 and its extension study, 39% of TEGSEDI-treated patients with a baseline platelet count below  $200 \times 10^9/L$  had a nadir platelet count below  $75 \times 10^9/L$ , compared to 6% of patients with baseline platelet counts  $200 \times 10^9/L$  or higher.

Three TEGSEDI-treated patients (3%) had sudden severe thrombocytopenia (platelet count below  $25 \times 10^9/L$ ), which can have potentially fatal bleeding complications, including

spontaneous intracranial or intrapulmonary hemorrhage. One patient in a clinical trial experienced a fatal intracranial hemorrhage.

In clinical trials, all 3 patients with severe thrombocytopenia had treatment-emergent antiplatelet IgG antibodies detected shortly before or at the time of the severe thrombocytopenia. In 2 patients, platelet clumping caused uninterpretable platelet measurements that delayed the diagnosis and treatment of severe thrombocytopenia. Platelet clumping can be caused by a reaction between antiplatelet antibodies and ethylenediaminetetraacetic acid (EDTA) [see *Warnings and Precautions (5.8)*].

### Monitoring and Dosing

Patients who are not able to adhere to the recommended laboratory monitoring or to the related treatment recommendations must not receive TEGSEDI. Do not initiate TEGSEDI in patients with a platelet count below  $100 \times 10^9/L$ . Follow recommended monitoring and treatment recommendations for platelet count [see *Dosage and Administration (2.4)*]. If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible, and hold TEGSEDI dosing unless the platelet count is confirmed to be acceptable. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable (e.g., clumped sample) [see *Warnings and Precautions (5.8)*]. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

### Concomitant Medications with Platelet Effects

When considering use of TEGSEDI concomitantly with antiplatelet drugs or anticoagulants, be aware of the risk of potential bleeding from thrombocytopenia with TEGSEDI, and consider discontinuation of these drugs in patients with a platelet count less than  $50 \times 10^9/L$  [see *Drug Interactions (7.1)*].

### Symptoms of Thrombocytopenia

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (e.g., 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.

### Severe Thrombocytopenia: Treatment with Glucocorticoids

Glucocorticoid therapy is strongly recommended in patients with a platelet count below  $50 \times 10^9/L$ , and in patients with suspected immune-mediated thrombocytopenia. Avoid using TEGSEDI in patients for whom glucocorticoid treatment is not advised.

## **5.2 Glomerulonephritis and Renal Toxicity**

TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1 [see *Clinical studies (14)*], glomerulonephritis occurred in three (3%) TEGSEDI-treated patients vs. no patient on placebo. In these patients, stopping TEGSEDI alone was not sufficient to resolve manifestations of glomerulonephritis, and treatment with an immunosuppressive medication was necessary. 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.

Cases of glomerulonephritis were accompanied by nephrotic syndrome. Possible complications of nephrotic syndrome can include edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection. TEGSEDI-treated patients who develop glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations.

Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, sometimes leading to increased tubular proteinuria, has been described in nonclinical studies. Urine protein to creatinine ratio (UPCR) greater than 5 times the upper limit of normal occurred in 15% of TEGSEDI-treated patients, compared to 8% of patients on placebo. Increase from baseline in serum creatinine greater than 0.5 mg/dL occurred in 11% of TEGSEDI-treated patients, compared to 2% of patients on placebo.

Follow recommended monitoring and treatment recommendations for renal parameters [*see Dosage and Administration (2.4)*]. 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 [*see Contraindications (4)*].

Use caution with nephrotoxic drugs and other drugs that may impair renal function. Because immunosuppressive treatment is necessary for the treatment of glomerulonephritis, avoid using TEGSEDI in patients for whom immunosuppressive treatment is not advised.

### **5.3 TEGSEDI REMS Program**

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 [*see Warnings and Precautions (5.1, 5.2)*].

Important requirements of the TEGSEDI Prescribing Program include:

- Prescribers must be certified within the program by enrolling and completing training.
- Patients must enroll in the program and comply with ongoing monitoring requirements [*see Warnings and Precautions (5.1) and Dosage and Administration (2.4)*]. Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive TEGSEDI.

Further information, including a list of qualified pharmacies/distributors, is available at [www.TEGSEDIREMS.com](http://www.TEGSEDIREMS.com) or 1-844-483-4736.

### **5.4 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. These events occurred within 2 days of the first TEGSEDI dose, a time when the patient also had symptoms of cytokine release (e.g., nausea, vomiting, muscular pain and weakness) and a high sensitivity C-reactive protein level greater than 100 mg/L.

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.

## **5.5 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 [see *Warnings and Precautions (5.2) and (5.3)*].

### **Neurologic Serious Adverse Reactions**

In clinical studies, neurologic serious adverse reactions consistent with inflammatory and immune effects occurred in TEGSEDI-treated patients, in addition to stroke and carotid artery dissection [see *Warnings and Precautions (5.5)*]. Two months after the first TEGSEDI dose, one patient developed a change in gait that progressed over 6 months to paraparesis, in the absence of radiologic evidence of spinal cord compression. Another patient developed progressive lumbar pain, weight loss, headache, vomiting, and impaired speech 7 months after starting TEGSEDI. Cerebrospinal fluid analysis findings included elevated protein, a lymphocyte-predominant pleocytosis, and testing that was negative for infection. The patient recovered after empiric therapy (high-dose steroids, antibiotics) and resumed TEGSEDI without recurrence of symptoms.

## **5.6 Liver Effects**

The liver is a site of accumulation of antisense oligonucleotides. 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 to 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN, compared to no patient on placebo. Some patients had resolution of the liver laboratory abnormalities with continued use of TEGSEDI.

In clinical studies, demonstrated or possible cases of immune-mediated biliary disease occurred in TEGSEDI-treated patients. There was a single case of autoimmune hepatitis with primary biliary cirrhosis in a patient with a family history of primary biliary cirrhosis, as well as a single case of biliary obstruction of unclear etiology.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin at baseline and every four months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.

## **5.7 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. Antibodies to TEGSEDI were present when the reactions occurred. These reactions generally occurred within

2 hours of administration of TEGSEDI and included headache, chest pain, hypertension, chills, flushing, dysphagia, palmar erythema, eosinophilia, involuntary choreiform movements, arthralgia, myalgia, and flu-like symptoms.

If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI, and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reaction to TEGSEDI.

### **5.8 Uninterpretable Platelet Counts: Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid (EDTA)**

In Study 1 [see *Clinical Studies (14)*], 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping, compared to 13% of patients on placebo. In 2 cases of severe thrombocytopenia with platelet count below  $25 \times 10^9/L$ , one of which resulted in death, clumped platelet samples caused a delay in diagnosis and treatment. Both subjects had tested positive for treatment-emergent anti-platelet IgG antibodies detected shortly before, or at the time of the severe reduction in platelet count.

Although platelet clumping can have a variety of causes (e.g., incompletely mixed or inadequately anticoagulated samples), platelet clumping can be caused by a reaction between antiplatelet antibodies and ethylenediaminetetra-acetic acid (EDTA). In Study 1, 7 of the 9 (78%) TEGSEDI-treated patients with treatment-emergent positive antiplatelet antibody testing had at least 1 clumped platelet sample.

If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (e.g., 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.

### **5.9 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. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with TEGSEDI, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

## **6 ADVERSE REACTIONS**

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Thrombocytopenia [see *Warnings and Precautions (5.1)*]
- Glomerulonephritis and Renal Toxicity [see *Warnings and Precautions (5.2)*]
- Stroke and Cervicocephalic Arterial Dissection [see *Warnings and Precautions (5.4)*]

- Inflammatory and Immune Effects [*see Warnings and Precautions (5.5)*]
- Liver Effects [*see Warnings and Precautions (5.6)*]
- Hypersensitivity [*see Warnings and Precautions (5.7)*]
- Reduced Serum Vitamin A Levels and Recommended Supplementation [*see Warnings and Precautions (5.9)*]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of TEGSEDI cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

A total of 112 adult patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR) received TEGSEDI in Study 1 and 60 patients received placebo. The mean age of the study patients was 59 years (27 to 78 years of age). Of the TEGSEDI-treated patients, 69% were male and 94% were Caucasian, with a mean exposure of 385 days, and median exposure of 449 days. Baseline disease characteristics were largely similar in TEGSEDI-treated patients and patients in the placebo control group. Sixty-seven percent of patients were in Stage 1 of the disease at baseline, and 33% in Stage 2. Fifty-two percent of patients had Val30Met mutations in the TTR gene, with the remaining 48% comprised of 26 different other point mutations.

[Table 2](#) presents common adverse reactions that occurred in at least 5% of TEGSEDI-treated patients and that occurred at least 5% more frequently or two times more frequently than on placebo.

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than 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%). The most common adverse reactions leading to discontinuation were thrombocytopenia and cachexia.

**Table 2: Adverse Reactions Reported in At Least 5% TEGSEDI-Treated Patients and that Occurred At Least 5% More Frequently or At Least Two Times More Frequently than Placebo Patients (Study 1)**

	TEGSEDI (N=112) %	Placebo (N=60) %
Injection site reactions <sup>a</sup>	49	10
Nausea	31	12
Headache	26	12
Fatigue	25	20
Thrombocytopenia	24	2
Fever	20	8
Peripheral edema	19	10
Chills	18	3
Anemia	17	3
Vomiting	15	5
Myalgia	15	10
Decreased renal function	14	5
Arrhythmia <sup>b</sup>	13	5
Arthralgia	13	8
Pre-syncope or syncope	13	5
Decreased appetite	10	0
Paresthesia	10	3
Dyspnea	9	3
Elevated liver function test	9	3
Orthostasis	8	2
Influenza like illness	8	3
Contusion	7	2
Bacterial infection <sup>c</sup>	7	3

Eosinophilia	5	0
Dry mouth	5	2

<sup>a</sup> Includes bruising, erythema, hematoma, hemorrhage, induration, inflammation, mass, edema, pain, pruritus, rash, swelling, and urticaria.

<sup>b</sup> Includes arrhythmia, atrial fibrillation, atrial flutter, bradyarrhythmia, bradycardia, extrasystoles, sinus arrhythmia, sinus bradycardia, supraventricular extrasystoles, tachycardia, and ventricular extrasystoles.

<sup>c</sup> Includes bacteremia, cellulitis staphylococcal, clostridium difficile infection, conjunctivitis bacterial, cystitis Escherichia, *Helicobacter* gastritis, *Helicobacter* infection, Staphylococcal infection.

## 6.2 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TEGSEDI in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In Study 1, 30% of TEGSEDI-treated patients tested positive for anti-drug antibodies (ADA) following 65 weeks of treatment [see *Warnings and Precautions (5.7, 5.8)*]. However, the assay measured only IgG isotypes and the existence of other isotypes may be possible. In many cases adverse reactions occurred in patients with ADA, although the available data are too limited to make definitive conclusions about the relationship.

## 7 DRUG INTERACTIONS

### 7.1 Antiplatelet Drugs or Anticoagulant Medications

Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (e.g., adenosine, clopidogrel, prasugrel, ticagrelor, or ticlopidine), including non-prescription products that affect platelets (e.g., aspirin, nonsteroidal anti-inflammatory drugs), or anticoagulants (e.g., heparin, warfarin), concomitantly with TEGSEDI [see *Warnings and Precautions (5.1)*].

### 7.2 Nephrotoxic Drugs

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 [see *Warnings and Precautions (5.2)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no data on the developmental risk associated with the use of TEGSEDI use in pregnant women. TEGSEDI treatment leads to a decrease in serum vitamin A levels, and vitamin A

supplementation is advised for patients taking TEGSEDI. Vitamin A is essential for normal embryofetal development; however, excessive levels of Vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by TEGSEDI and of vitamin A supplementation are unknown [see *Clinical Pharmacology (12.2), Warnings and Precautions (5.9)*].

In animal studies, subcutaneous administration of inotersen to pregnant rabbits resulted in premature delivery and reduced fetal body weight at the highest dose tested, which was associated with maternal toxicity. No adverse developmental effects were observed when inotersen or a pharmacologically-active surrogate was administered to pregnant mice.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

## Data

### *Animal Data*

Subcutaneous administration of inotersen (0, 3, 15, or 25 mg/kg) or a rodent-specific surrogate (15 mg/kg) to male and female mice every other day prior to and during mating and continuing in females throughout the period of organogenesis produced no adverse effects on embryofetal development.

Subcutaneous administration of inotersen (0, 2.5, 5, or 15 mg/kg) to pregnant rabbits every other day throughout the period of organogenesis resulted in premature delivery and reduced fetal body weight at the highest dose tested, which was associated with maternal toxicity (reduced body weight and food consumption).

Subcutaneous administration of inotersen (0, 2.9, 11.4, or 22.9 mg/kg) or a rodent-specific surrogate (11.4 mg/kg) to mice every other day throughout pregnancy and lactation produced no adverse effects on pre- or postnatal development.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of TEGSEDI in human milk, the effects on the breast-fed infant, or the effects on milk production. A study in lactating mice has shown excretion of inotersen in milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for TEGSEDI and any potential adverse effects on the breastfed infant from TEGSEDI or from the underlying maternal condition.

## **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

## **8.5 Geriatric Use**

Clinical studies of TEGSEDI included 69 patients (45%) aged 65 and over. No differences in pharmacokinetics or effectiveness were observed between these patients and younger patients.

Patients 65 years and older may be at increased risk of certain adverse reactions, such as congestive heart failure, chills, myalgia, and extremity pain.

## 8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR]  $\geq 30$  to  $< 90$  mL/min/1.73m<sup>2</sup>) [see *Clinical Pharmacology (12.3)*]. TEGSEDI has not been studied in patients with severe renal impairment or end-stage renal disease.

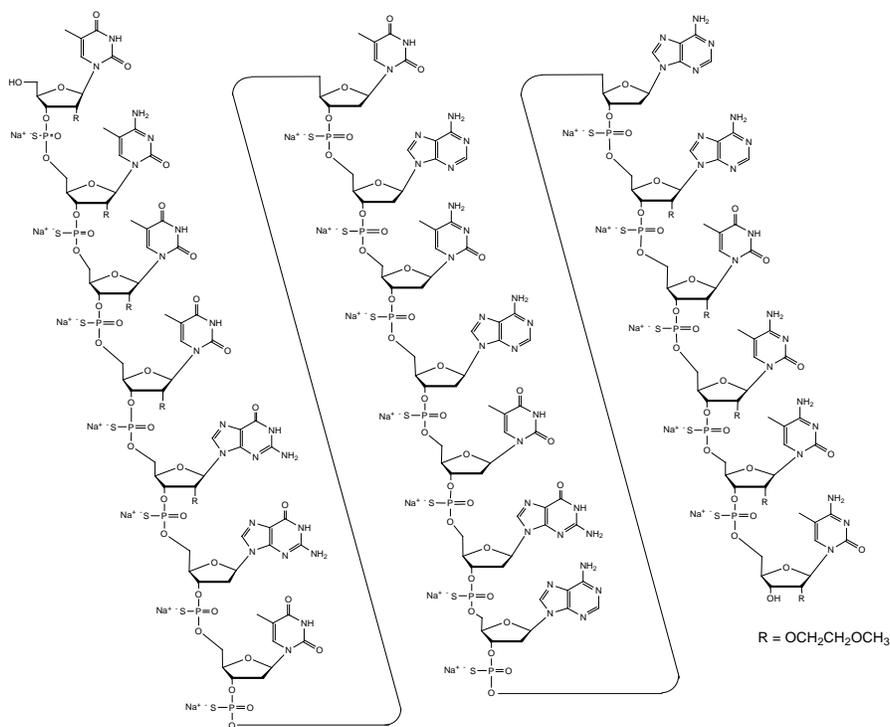
## 8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment [see *Clinical Pharmacology (12.3)*]. TEGSEDI has not been studied in patients with other degrees of hepatic impairment.

## 11 DESCRIPTION

Inotersen is an antisense oligonucleotide (ASO) inhibitor of human transthyretin (TTR) protein synthesis.

TEGSEDI contains inotersen sodium as the active ingredient. Inotersen sodium is a white to pale yellow solid and it is freely soluble in water and in phosphate buffer (pH 7.5 to 8.5). The chemical name of inotersen sodium is DNA, d(*P*-thio)([2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rU-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rC-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rU-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rU-[2'-*O*-(2-methoxyethyl)]rG-G-T-T-A-m<sup>5</sup>C-A-T-G-A-A-[2'-*O*-(2-methoxyethyl)]rA-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rU-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rC-[2'-*O*-(2-methoxyethyl)]m<sup>5</sup>rC). The molecular formula of inotersen sodium is C<sub>230</sub>H<sub>299</sub>N<sub>69</sub>Na<sub>19</sub>O<sub>121</sub>P<sub>19</sub>S<sub>19</sub> and the molecular weight is 7600.73 Da. It has the following structural formula:



The molecular formula of inotersen free base is C<sub>230</sub>H<sub>318</sub>N<sub>69</sub>O<sub>121</sub>P<sub>19</sub>S<sub>19</sub> and its molecular weight is 7183.08.

TEGSEDI is a sterile, preservative-free, aqueous solution for subcutaneous injection. It is supplied in a prefilled syringe (PFS). Each PFS contains 1.5 mL of solution containing 284 mg inotersen (equivalent to 300 mg inotersen sodium salt) TEGSEDI is formulated in Water for Injection and may include hydrochloric acid and/or sodium hydroxide for pH adjustment to 7.5-8.5.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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.

### 12.2 Pharmacodynamics

The pharmacodynamic effects of TEGSEDI were evaluated in hATTR amyloidosis patients treated with 284 mg TEGSEDI via subcutaneous injection once weekly.

With repeat dosing, the mean percent decreases from baseline in serum TTR from Week 13 to Week 65 of treatment ranged from 68% to 74% (median range: 75% to 79%). Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race.

Serum TTR is a carrier of retinol binding protein, which is involved in the transport of vitamin A in the blood. Mean reductions in serum retinol binding of 71%, and serum vitamin A of 63%, were observed at Week 65 [see *Warnings and Precautions* (5.6)].

### Cardiac Electrophysiology

Formal QTc studies have not been conducted with TEGSEDI. The potential for QTc prolongation with inotersen was evaluated in a randomized, placebo-controlled trial in healthy volunteers. No large changes in the mean QTc interval (>20 ms) were detected in the trial.

In the 66-week controlled efficacy trial, 5.4% of TEGSEDI-treated patients had evidence of QRS prolongation on their electrocardiograms (ECGs) to greater than 160 msec and greater than 25% above baseline, compared to and in 1.7% of patients on placebo.

### **12.3 Pharmacokinetics**

Following subcutaneous administration, systemic exposure to inotersen increase in a dose-proportional manner over the range of 150-400 mg of inotersen sodium salt. At the recommended TEGSEDI dosing regimen of 284 mg every week, steady state is reached after approximately 3 months. The estimated geometric mean (90% confidence interval) steady state peak concentrations (C<sub>max</sub>), trough concentrations (C<sub>trough</sub>), and area under the curve (AUC<sub>τ</sub>) were 6.39 (5.65, 7.20) µg/mL, 0.034 (0.031, 0.038) µg/mL, and 90 (82.4, 97.4) µg·h/mL, respectively. Plasma C<sub>max</sub> and AUC do not exhibit accumulation at steady state.

#### Absorption

Following subcutaneous administration, TEGSEDI is absorbed rapidly into systemic circulation in a dose-dependent fashion, with the median time to maximum plasma concentrations (C<sub>max</sub>) of 2 to 4 hours.

#### Distribution

TEGSEDI is highly bound to human plasma proteins (>94%) and the fraction bound is independent of drug concentration. Based on animal studies (mouse, rat and monkey), TEGSEDI rapidly distributes broadly to tissues, with the highest concentrations observed in the kidney and liver. TEGSEDI does not cross the blood-brain barrier. The apparent volume of distribution of TEGSEDI at steady-state (mean and 90% confidence interval) is 293 (268, 320) L in patients with hATTR.

#### Elimination

The terminal elimination half-life (mean and 90% confidence interval) for TEGSEDI is 32.3 (29.4, 35.5) days. Inotersen is mainly cleared through metabolism, and the total body clearance (mean and 90% confidence interval) is 3.18 (3.08, 3.29) L/h.

#### *Metabolism*

Inotersen is metabolized by nucleases to nucleotides of various lengths.

#### *Excretion*

Less than 1% of the administered dose of inotersen is excreted unchanged into urine within 24 hours.

## Specific Populations

Age, race, and sex had no impact on the steady state pharmacokinetics of inotersen or TTR reduction. Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR  $\geq$ 30 to  $<$ 90 mL/min/1.73m<sup>2</sup>) or mild hepatic impairment (bilirubin less than or equal to 1.5 x ULN and/or AST less than 1.9 x ULN) on inotersen exposure or TTR reduction. TEGSEDI has not been studied in patients with severe renal impairment, end-stage renal disease, moderate or severe hepatic impairment, or in patients with prior liver transplant.

## Drug Interaction Studies

No formal clinical drug interaction studies have been performed. TEGSEDI is not a substrate or inhibitor/inducer of major CYP enzymes or a substrate or inhibitor of major transporters. In a population pharmacokinetic analysis, concomitant use of diuretics, antithrombotic, and analgesics did not impact the pharmacokinetic parameters of inotersen. TEGSEDI is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 26-week carcinogenicity study in transgenic (TgRasH2) mice, weekly subcutaneous administration of inotersen (0, 10, 30, or 80 mg/kg) or a rodent-specific (pharmacologically active) surrogate (30 mg/kg) did not result in an increase in tumors.

Inotersen was negative for genotoxicity in *in vitro* (bacterial mutagenicity, chromosomal aberration in Chinese hamster lung) and *in vivo* (mouse bone marrow micronucleus) assays.

Subcutaneous administration of inotersen (0, 3, 15, or 25 mg/kg) or a rodent-specific surrogate (15 mg/kg) to male and female mice every other day prior to and during mating and continuing in females throughout the period of organogenesis produced no adverse effects on fertility.

## **14 CLINICAL STUDIES**

The efficacy of TEGSEDI was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT 01737398). Patients were randomized in a 2:1 ratio to receive either TEGSEDI (284 mg inotersen) (N=113) or placebo (N=60), respectively, as a subcutaneous injection administered once per week for 65 weeks (3 doses were administered during the first week of treatment). Seventy seven percent of TEGSEDI-treated patients and 87% of patients on placebo completed 66 weeks of the assigned treatment.

The co-primary efficacy endpoints were the change from baseline to Week 66 in the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score and the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score.

The mNIS+7 is an objective assessment of neuropathy, and comprises the NIS and Modified +7 composite scores. In the version of the mNIS+7 used in the trial, the NIS objectively measures

deficits in cranial nerve function, muscle strength, reflexes, and sensations, and the Modified +7 assesses heart rate response to deep breathing, postural blood pressure, quantitative sensory testing (touch-pressure and heat-pain), and peripheral nerve electrophysiology. The maximum possible score was 346.32 points, with higher scores representing a greater severity of disease.

The clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Week 66 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial had a maximum possible total score of 136 points, with higher scores representing greater impairment.

The changes from baseline to Week 66 on both the mNIS+7 and the Norfolk QoL-DN significantly favored TEGSEDI (Table 3, Figures 1 and 3). The distributions of changes in mNIS+7 and Norfolk QoL-DN scores from baseline to Week 66 by percent of patients are shown in Figure 2 and Figure 4, respectively.

**Table 3: Clinical Efficacy Results from Study 1**

Endpoint	Baseline		Change from Baseline to Week 66 (LS Mean)		TEGSEDI – placebo Treatment Difference LS Mean (95% CI)	p-value
	TEGSEDI	Placebo	TEGSEDI	Placebo		
<b>Primary<sup>a</sup></b>						
mNIS+7 <sup>b, c</sup>	80.2	75.3	5.8	25.5	-19.7 [-26.4, -13.0]	<0.001
Norfolk QOL-DN <sup>b, d</sup>	48.7	48.7	1.0	12.7	-11.7 [-18.3, -5.1]	<0.001

CI, confidence interval; LS, least squares; mNIS, modified Neuropathy Impairment Score; QoL-DN, Quality of Life – Diabetic Neuropathy

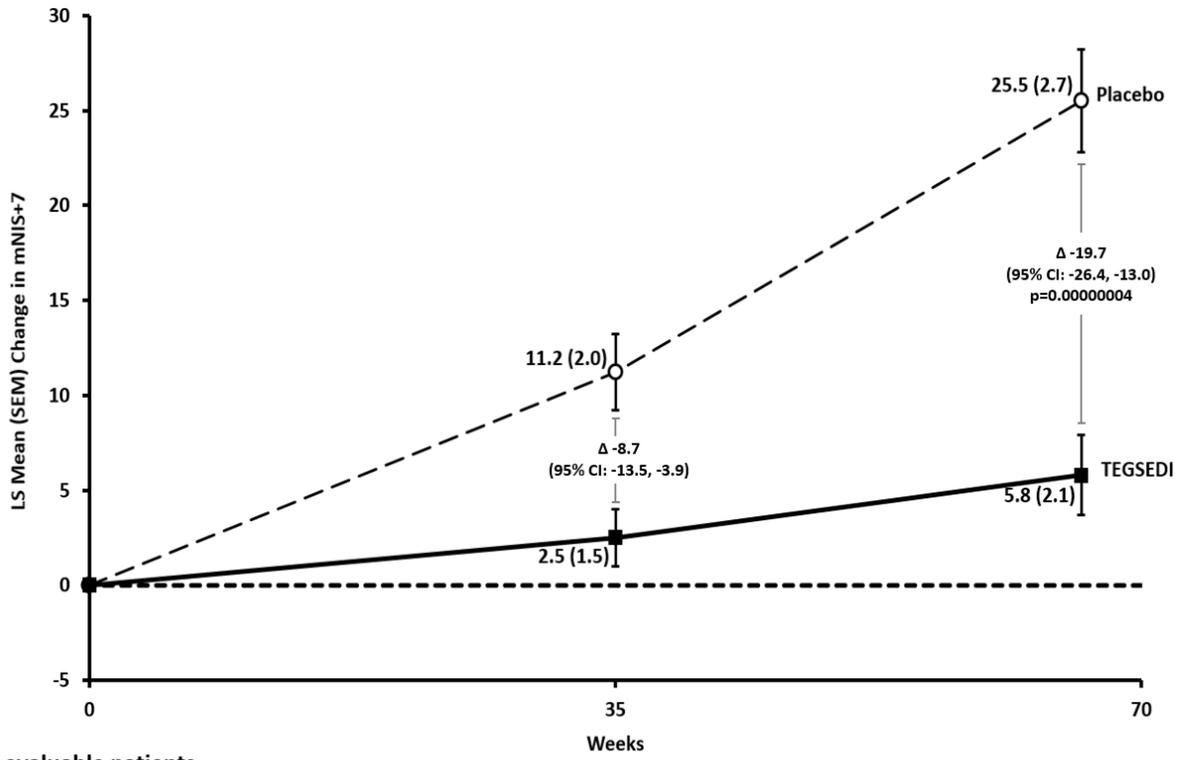
<sup>a</sup> All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.

<sup>b</sup> A lower value indicates less impairment/fewer symptoms.

<sup>c</sup> The primary analysis population for the mNIS+7 analysis included N=95 TEGSEDI patients and N=56 placebo patients

<sup>d</sup> The primary analysis population for the Norfolk QOL-DN analysis included N=94 TEGSEDI patients and N=57 placebo patients

Figure 1: Change from Baseline in mNIS+7



**N of evaluable patients**

Placebo	59	55	52
TEGSEDI	106	95	85

**Figure 2: Histogram of mNIS+7 Change from Baseline at Week 66**

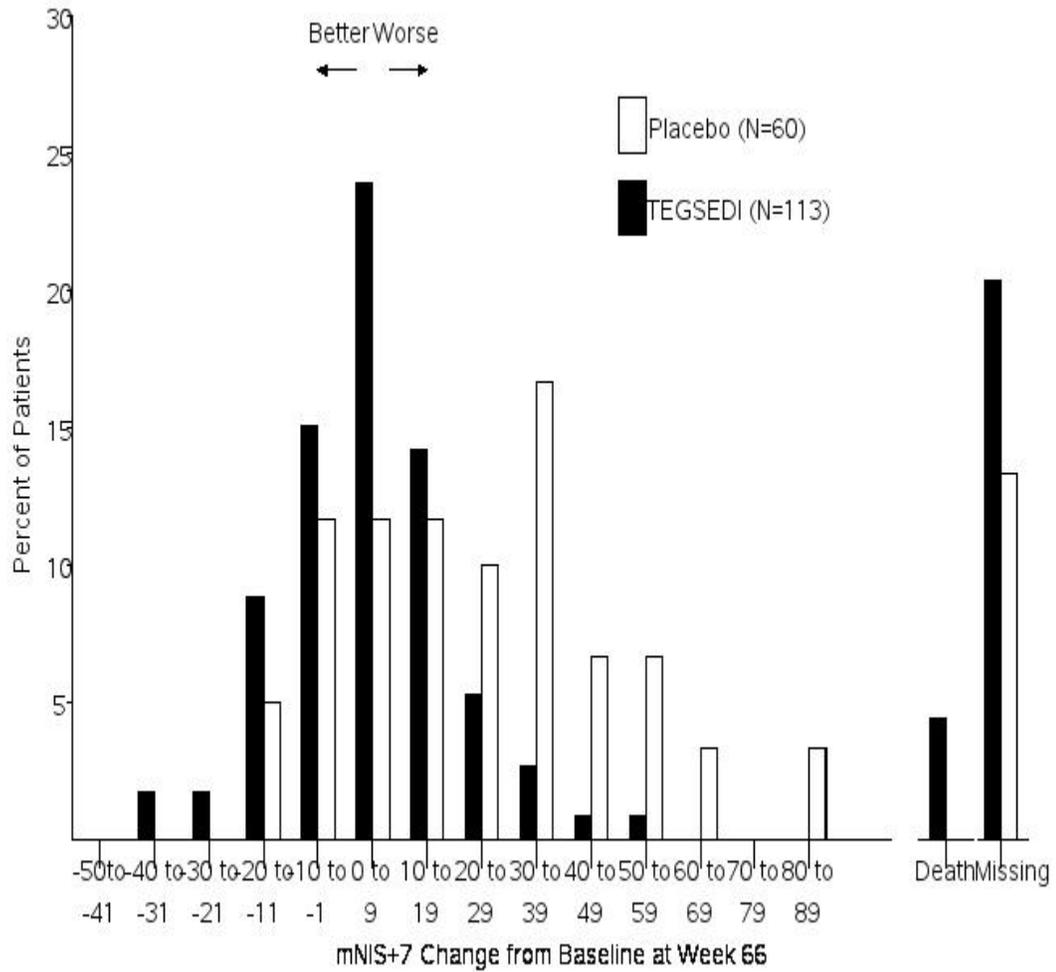
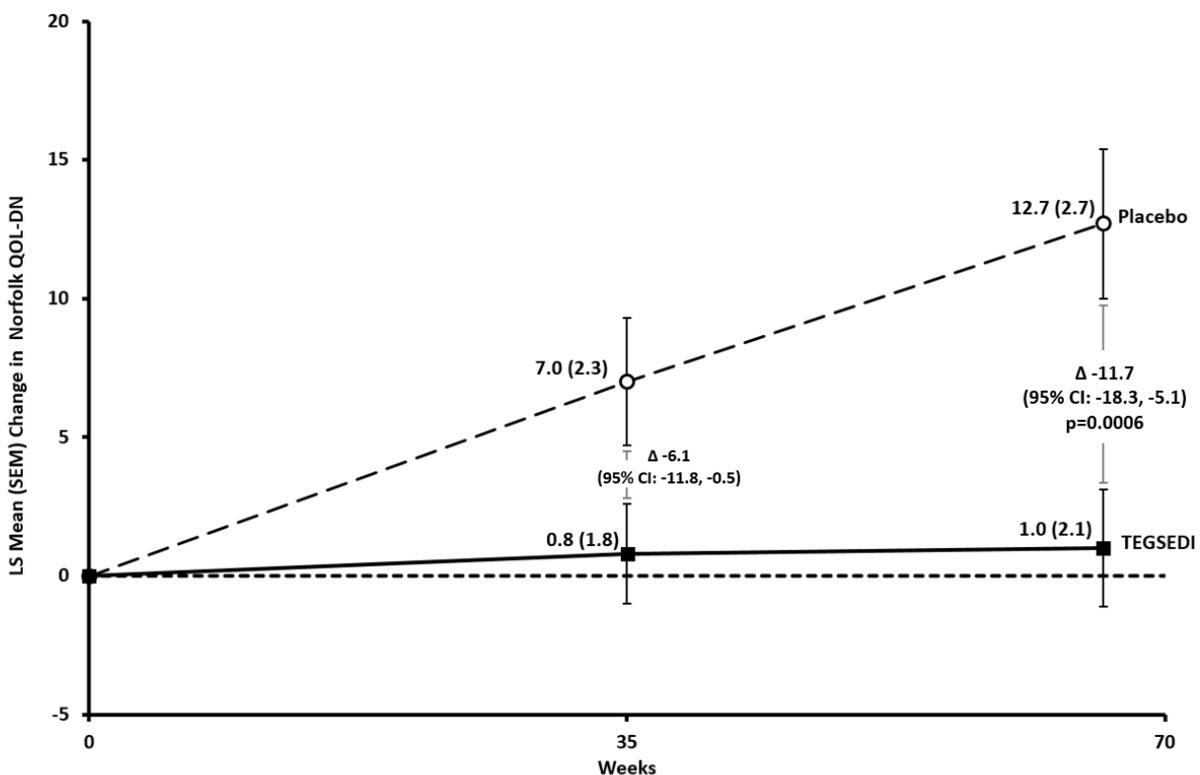


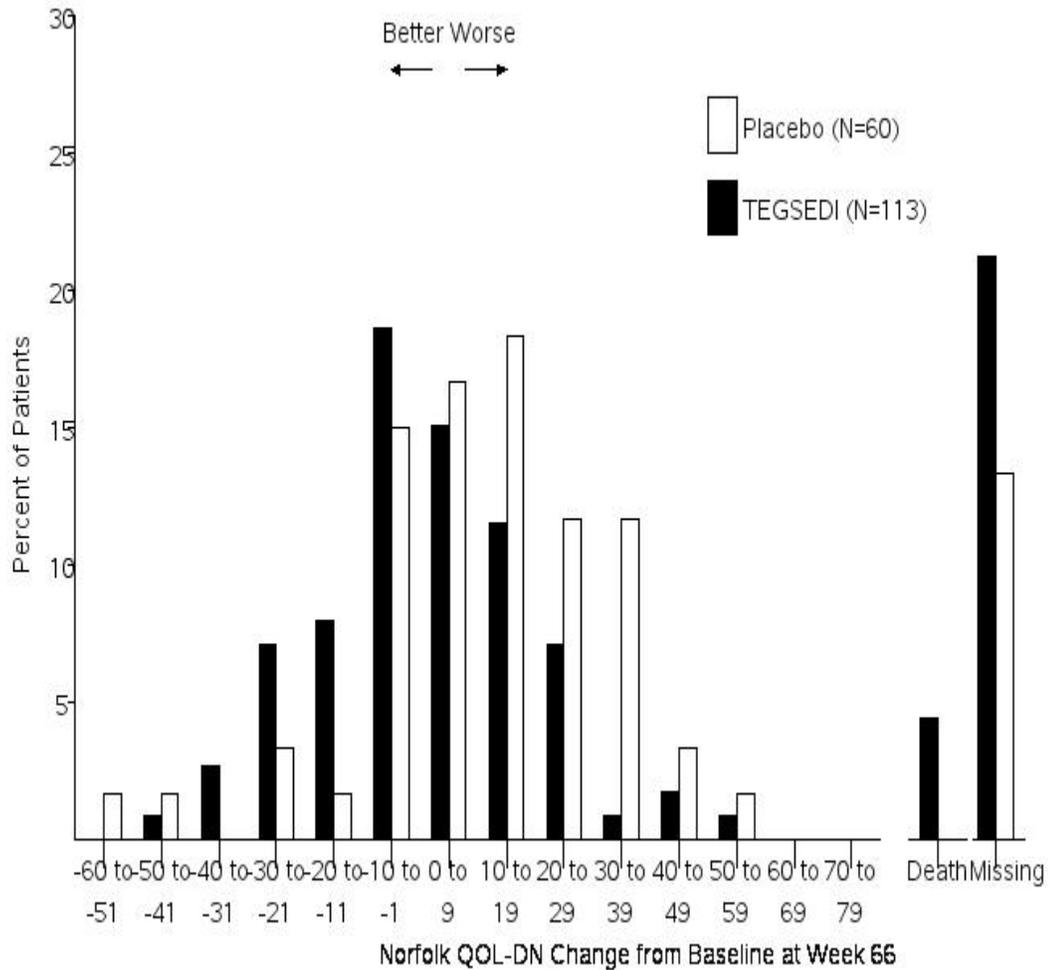
Figure 3: Change from Baseline in Norfolk QoL-DN Score



**N of evaluable patients**

Placebo	58	57	52
TEGSEDI	105	94	84

**Figure 4: Histogram of Norfolk QoL-DN Change from Baseline at Week 66**



Patients receiving TEGSEDI experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

TEGSEDI is a clear, colorless to pale yellow solution supplied in a single-dose, prefilled syringe with a SSD. Each prefilled syringe of TEGSEDI is filled to deliver 1.5 mL of solution containing 284 mg of inotersen (equivalent to 300 mg inotersen sodium salt).

TEGSEDI is available in cartons containing 1 or 4 prefilled syringes.

- Pack of 1 prefilled syringe: NDC 72126-007-03
- Pack of 4 prefilled syringes: NDC 72126-007-01

The Individual Tray contains NDC 72126-007-02.

### Pharmacy

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container and protect from direct light. Do not freeze.

### For Patients/Caregivers

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container. Do not freeze.

TEGSEDI can be kept at room temperature (up to 30°C [86°F]) in the original container for up to 6 weeks; if not used within the 6 weeks, discard TEGSEDI.

Remove from refrigerated storage (2°C to 8°C [36°F to 46°F]) at least 30 minutes before use. [TEGSEDI] prefilled syringe should be allowed to reach room temperature prior to injection.

Avoid exposure to temperatures above 30°C (86°F).

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient and caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Thrombocytopenia

Inform patients that TEGSEDI can cause reductions in platelet count that may result in thrombocytopenia. Instruct patients to notify a healthcare provider immediately if they show symptoms of thrombocytopenia (e.g., unusual or prolonged bleeding, neck stiffness, or atypical severe headache). Advise patients of the importance of monitoring during treatment with TEGSEDI [*see Warnings and Precautions (5.1)*]. Also instruct patients to notify their healthcare provider of all medications, including over-the-counter, that they are taking [*see Drug Interactions (7.1)*].

### Glomerulonephritis and Renal Toxicity

Inform patients that glomerulonephritis has occurred in patients treated with TEGSEDI. Advise patients of the importance of monitoring of urine protein to creatinine ratio (UPCR) during treatment with TEGSEDI [*see Warnings and Precautions (5.2)*].

### TEGSEDI REMS Program

TEGSEDI is available only through a restricted program called the TEGSEDI REMS Program [*see Warnings and Precautions (5.3)*]. Inform the patient of the following notable requirements:

- Patients must enroll in the program and comply with ongoing monitoring requirements.
- TEGSEDI is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

### Stroke and Cervicocephalic Arterial Dissection

Educate patient on symptoms of stroke and central nervous system arterial dissection and instruct them to seek help as soon as possible if symptoms of these or other serious neurologic adverse reactions occur [*see Warnings and Precautions (5.4)*].

### Liver Effects

Instruct patients to inform a healthcare professional of symptoms suggestive of hepatic dysfunction that occur after administration of TEGSEDI [*see Warnings and Precautions (5.6)*].

### Hypersensitivity

Instruct patients to inform a healthcare professional of symptoms suggestive of hypersensitivity that occur after administration of TEGSEDI [*see Warnings and Precautions (5.7)*].

### Recommended Vitamin A Supplementation

Inform patients that TEGSEDI treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [*see Warnings and Precautions (5.9)*].

### Administration Instructions

Train patients and caregivers on proper subcutaneous administration technique and how to use the single-dose prefilled syringe. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use TEGSEDI.

### Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking TEGSEDI they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus [*see Use in Specific Populations (8.1)*].

For more information about TEGSEDI, go to [www.TEGSEDIREMS.com](http://www.TEGSEDIREMS.com) or call 1-844-483-4736.

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