TEGSEDI® REMS
Prescriber Training

What is TEGSEDI?

TEGSEDI is an antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Risk of serious bleeding with severe thrombocytopenia and risk of glomerulonephritis

- TEGSEDI may cause serious bleeding with severe thrombocytopenia
- TEGSEDI must not be initiated in patients with a platelet count less than 100 × 10^9/L
- TEGSEDI can cause glomerulonephritis. It should not normally be initiated in patients with a urine protein to creatinine ratio of 1000 mg/g or higher

Thrombocytopenia

TEGSEDI causes reductions in platelet count at any time during treatment that may result in thrombocytopenia that may be severe and result in serious bleeding. Examples of serious bleeding include fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin of 2 g/dL or more within 24 hours, or bleeding leading to blood transfusion.

The signs and symptoms of thrombocytopenia 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 the gums or nose
- Blood in urine or stools
- Bleeding into the whites of eyes
- Sudden severe headaches or neck stiffness
- Vomiting blood or coughing up blood
- Abnormal or heavy menstrual periods

Thrombocytopenia can be life threatening and can occur quickly; inform your patients of the importance of monitoring, the signs and symptoms of thrombocytopenia and serious bleeding, and to notify you or another healthcare provider immediately if they show signs or symptoms.

Follow the monitoring and treatment recommendations for platelet count in the Prescribing Information. 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. Re-check the platelet count as soon as possible if a platelet measurement is uninterpretable (e.g., clumped sample). Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

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

Follow thrombocytopenia monitoring and treatment recommendations in the Prescribing Information.

Glomerulonephritis

TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. The signs and symptoms of glomerulonephritis include:

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

Inform your patients of the importance of monitoring, the signs and symptoms of glomerulonephritis, and to notify a healthcare provider immediately if they show signs or symptoms.

Follow the monitoring and treatment recommendations for renal parameters in the Prescribing Information.

If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.

What is the TEGSEDI REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential risks associated with a drug, and is required by the Food and Drug Administration (FDA) to ensure the benefits of the drug outweigh its risks.

Because of the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis, TEGSEDI is available only under a restricted program called the TEGSEDI REMS. The goal of the TEGSEDI REMS is to mitigate these risks by:

- Ensuring prescribers are educated on the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with TEGSEDI
- Ensuring prescribers are educated and adhere to the following:
  - Counseling patients on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
  - Enrolling patients in the TEGSEDI REMS
  - Submit documentation that periodic monitoring of patients is being done to identify severe thrombocytopenia, serious bleeding with severe thrombocytopenia and glomerulonephritis
- Ensuring patients are informed on the following:
  - How to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
  - The need to have platelet count and renal function monitored
- Enrollment of all patients in a registry (i.e. enrolling in the REMS) to further support long-term safety and safe use of TEGSEDI

Tegsedi® (inotersen) injection 284 mg/1.5 mL

TEGSEDI® REMS

Prescriber Training

How does a prescriber become certified in the TEGSEDI REMS?

- Review the TEGSEDI Prescribing Information, *REMS Program Overview*, and *Prescriber Training*
- Successfully complete the *Prescriber Knowledge Assessment* and submit it to the REMS
- Enroll in the REMS by completing the *Prescriber Enrollment Form* and submitting it to the REMS

You will not be able to prescribe TEGSEDI without completing your certification in the TEGSEDI REMS.

Prescriber requirements

Before treatment initiation (first dose):

- Counsel the patient on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis and the need to have their platelet count and renal function monitored, using the *Patient Guide* and *Wallet Card*
- Provide the patient with the *Patient Guide* and *Wallet Card*
- Assess the patient's platelet count and appropriateness of initiating treatment. Document using the *Patient Enrollment Form*
- Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and appropriateness of initiating treatment. Document using the *Patient Enrollment Form*
- Enroll the patient by completing and submitting the *Patient Enrollment Form* to the REMS. Provide a completed copy of the form to the patient

During treatment:

Weekly or more frequently (as described in the Prescribing Information):

- Assess the patient's platelet count and appropriateness of continuing treatment

Every 2 weeks:

- Assess the patient's eGFR, urinalysis, UPCR, and appropriateness of continuing treatment

Every 90 days:

- Assess the patient's platelet count, signs and symptoms of thrombocytopenia, and appropriateness of continuing treatment. Document and submit to the REMS using the *Patient Status Form*
- Assess the patient's eGFR, urinalysis, UPCR, signs and symptoms of renal toxicity, and appropriateness of continuing treatment. Document and submit to the REMS using the *Patient Status Form*

At treatment discontinuation:

- Document treatment discontinuation and submit to the REMS using the *Patient Status Form*

After treatment discontinuation:

For 8 weeks:

- Assess the patient's platelet count weekly, or more frequently as described in the Prescribing Information
- Assess the patient's eGFR, urinalysis, UPCR, and risk of glomerulonephritis every 2 weeks

At 8 weeks:

- Assess the patient's platelet count and signs and symptoms of thrombocytopenia. Document and submit to the REMS documentation that you have performed monitoring and evaluation using the *Patient Status Form*
- Assess the patient's eGFR, urinalysis, UPCR, and signs and symptoms of renal toxicity. Document and submit to the REMS documentation that you have performed monitoring and evaluation using the *Patient Status Form*

At all times:

- Report severe thrombocytopenia, serious bleeding due to severe thrombocytopenia and glomerulonephritis to the REMS at 1-844-4TEGREMS (1-844-483-4736)
- Report other adverse events associated with TEGSEDI to Sobi, Inc., 1-833-642-5232 and/or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088
- Report treatment discontinuation or transfer of care to the REMS using the *Patient Status Form*

A summary of the prescriber requirements for the REMS patient assessment, monitoring and Patient Status Form submission is provided as a reference to this training in Appendix 1.

For more information about the TEGSEDI REMS, please visit www.TEGSEDIrems.com or call the TEGSEDI REMS Coordinating Center at 1-844-4TEGREMS (1-844-483-4736).

Please see the Prescribing Information for more information.

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Appendix 1 - Patient Status Form Timing Requirements Reminder Sheet

REMS Patient Assessment, Monitoring and Patient Status Form Submission

X Laboratory monitoring requirements X Patient assessment requirements X Patient Status Form requirements

	During treatment			Treatment Discontinuation	After treatment discontinuation			Change in Prescriber
	Weekly*	Every 2 weeks	Every 90 days	At time of treatment discontinuation	Weekly* for 8 weeks	Every 2 weeks for 8 weeks	At 8 weeks	When there is a change in prescriber or transfer of care
Assess the appropriateness of continuing treatment	**At all times while patient is receiving TEGSEDI**							
Monitor platelet count	X				X			
Monitor eGFR, urinalysis, and UPCR		X				X		
Assess signs and symptoms of thrombocytopenia	X	X	X**				X**	
Assess signs and symptoms of renal toxicity	X	X	X**				X**	
Submit a Patient Status Form to the REMS			X	X			X	X

*Platelet evaluations may be required more frequently than weekly as described in the Prescribing Information
** Include evaluation of the most recent laboratory monitoring to assess the signs and symptoms of thrombocytopenia and renal toxicity to ensure accurate reporting in the Patient Status Form