

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21172Orig1s000**

**REMS**

# Risk Evaluation and Mitigation Strategy (REMS) Document

## Tegsedi (inotersen) REMS Program

### I. Administrative Information

Application Number: NDA 211172  
Application Holder: Ionis Pharmaceuticals  
Initial REMS Approval: 10/2018

### II. REMS Goal

The goal of the Tegsedi REMS is to mitigate the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with Tegsedi by:

1. Ensuring prescribers are educated on the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with Tegsedi.
2. Ensuring prescribers are educated and adhere to the following:
  - a. Counsel patients on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis.
  - b. Enroll patients in the Tegsedi REMS Program.
  - c. Submit documentation that periodic monitoring of patients is being done to identify severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis.
3. Ensuring patients are informed on the following:
  - a. How to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis.
  - b. The need to have their platelet count and renal function monitored.
4. Enrollment of all patients in a registry to further support long-term safety and safe use of Tegsedi.

### III. REMS Requirements

**Ionis Pharmaceuticals must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:**

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#### 1. Healthcare providers who prescribe Tegsedi must:

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|----------------------------------|--|
| To become certified to prescribe | <ol style="list-style-type: none"><li>1. Review the drug's Prescribing Information.</li><li>2. Review the following: <a href="#">Prescriber Training</a> and <a href="#">Program Overview</a>.</li><li>3. Successfully complete the <a href="#">Prescriber Knowledge Assessment</a> and submit it to the REMS Program.</li><li>4. Enroll in the REMS by completing the <a href="#">Prescriber Enrollment Form</a> and submitting it to the REMS Program.</li></ol> |
|----------------------------------|--|
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Before treatment initiation (first dose)	<ol style="list-style-type: none"> <li>5. 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 <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</li> <li>6. Provide the patient with the <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</li> <li>7. Assess the patient's platelet count and appropriateness of initiating treatment. Document and submit to the REMS Program using the <a href="#">Patient Enrollment Form</a>.</li> <li>8. Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and appropriateness of initiating treatment. Document and submit to the REMS Program using the <a href="#">Patient Enrollment Form</a>.</li> <li>9. Enroll the patient by completing and submitting the <a href="#">Patient Enrollment Form</a> to the REMS Program. Provide a completed copy of the form to the patient.</li> </ol>
During treatment; weekly or more frequently as described in the Prescribing Information	<ol style="list-style-type: none"> <li>10. Assess the patient's platelet count and appropriateness of continuing treatment.</li> </ol>
During treatment; every two weeks	<ol style="list-style-type: none"> <li>11. Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and appropriateness of continuing treatment.</li> </ol>
During treatment; every 90 days	<ol style="list-style-type: none"> <li>12. Assess the patient's platelet count, signs and symptoms of thrombocytopenia, and appropriateness of continuing treatment. Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</li> <li>13. Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), signs and symptoms of renal toxicity, and appropriateness of continuing treatment. Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</li> </ol>
After treatment discontinuation; weekly for 8 weeks or more frequently as described in the Prescribing Information	<ol style="list-style-type: none"> <li>14. Assess the patient's platelet count.</li> </ol>
After treatment discontinuation; every 2 weeks for 8 weeks	<ol style="list-style-type: none"> <li>15. Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR).</li> </ol>
After treatment discontinuation; at 8 weeks	<ol style="list-style-type: none"> <li>16. Assess the patient's platelet count and signs and symptoms of thrombocytopenia. Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</li> <li>17. Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), and signs and symptoms of renal</li> </ol>

	toxicity. Document and submit to the REMS Program using the <a href="#">Patient Status Form</a> .
At all times	<p>18. Report events of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis to the REMS Program.</p> <p>19. Report treatment discontinuation or transfer of care to the REMS Program using the <a href="#">Patient Status Form</a>.</p>

## 2. Patients who are prescribed Tegsedi:

Before treatment initiation (first dose)	<ol style="list-style-type: none"> <li>1. Review the <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</li> <li>2. Enroll in the REMS Program by completing the <a href="#">Patient Enrollment Form</a> with the prescriber. Enrollment information will be provided to the REMS Program.</li> <li>3. Get a blood test to check your platelet count and blood and urine tests to check your kidneys.</li> <li>4. Receive counseling from the prescriber on the risk of serious bleeding, the risk of kidney inflammation (glomerulonephritis), and the need to complete the appropriate laboratory testing using the <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</li> </ol>
During treatment; every week or more often as directed by your prescriber	<ol style="list-style-type: none"> <li>5. Get a blood test to check your platelet count.</li> </ol>
During treatment; every two weeks	<ol style="list-style-type: none"> <li>6. Get blood and urine tests to check your kidneys.</li> </ol>
After treatment discontinuation; weekly for 8 weeks or more often as directed by your prescriber	<ol style="list-style-type: none"> <li>7. Get a blood test to check your platelet count.</li> </ol>
After treatment discontinuation; every 2 weeks for 8 weeks	<ol style="list-style-type: none"> <li>8. Get blood and urine tests to check your kidneys.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>9. Inform the prescriber if you have serious bleeding or signs and symptoms of kidney inflammation.</li> <li>10. Have the <a href="#">Wallet Card</a> with you.</li> <li>11. Inform all of your healthcare providers about this treatment.</li> </ol>

## 3. Pharmacies that dispense Tegsedi must:

To become certified to dispense	<ol style="list-style-type: none"> <li>1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.</li> </ol>
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	<ol style="list-style-type: none"> <li>2. Have the authorized representative review the <a href="#">Program Overview</a>.</li> <li>3. Have the authorized representative enroll in the REMS Program by completing the <a href="#">Pharmacy Enrollment Form</a> and submitting it to the REMS Program.</li> <li>4. Establish processes and procedures to dispense no more than a 30-days' supply.</li> <li>5. Establish processes and procedures to report severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis events to the REMS Program.</li> <li>6. Train all relevant staff involved in the dispensing of Tegsedi on the program requirements using the <a href="#">Program Overview</a>.</li> </ol>
Before dispensing	<ol style="list-style-type: none"> <li>7. Obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified and the patient is enrolled and authorized to receive the drug.</li> <li>8. Dispense no more than a 30days' supply.</li> </ol>
To maintain certification to dispense	<ol style="list-style-type: none"> <li>9. Have a new authorized representative enroll in the REMS Program by completing the <a href="#">Pharmacy Enrollment Form</a> and submitting it to the REMS Program if the authorized representative changes.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>10. Report severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis events to the REMS Program.</li> <li>11. Not distribute, transfer, loan, or sell Tegsedi, except to certified dispensers.</li> <li>12. Maintain records documenting staff's completion of REMS training.</li> <li>13. Maintain records that all REMS processes and procedures are in place and are being followed.</li> <li>14. Comply with audits carried out by Ionis Pharmaceuticals or a third party acting on behalf of Ionis Pharmaceuticals to ensure all processes and procedures are in place and are being followed.</li> </ol>

**4. Wholesalers-distributors that distribute Tegsedi must:**

To be able to distribute	<ol style="list-style-type: none"> <li>1. Establish processes and procedures to ensure the drug is distributed only to certified pharmacies.</li> <li>2. Train all relevant staff involved in distributing on the program requirements.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>3. Distribute only to certified pharmacies.</li> <li>4. Maintain records of all distributions.</li> <li>5. Comply with audits carried out by Ionis Pharmaceuticals or a third party acting on behalf of Ionis Pharmaceuticals to ensure all processes and procedures are in place and are being followed.</li> </ol>

**Ionis Pharmaceuticals must provide training to healthcare providers who prescribe Tegsedi.**

The training includes the following educational materials: [Prescriber Training](#), [Program Overview](#), and [Prescriber Knowledge Assessment](#). The training must be available online and by hard copy via fax or mail.

**Ionis Pharmaceuticals must provide training to pharmacies that dispense Tegsedi.**

The training includes the following educational material: [Program Overview](#). The training must be available online and by hard copy via fax or mail.

**To support REMS Program operations, Ionis Pharmaceuticals must:**

1. Authorize dispensing for each patient within every 90 calendar days but not later than every 115 calendar days from the date of first dispense of TEGSEDI documented by receipt of the [Patient Status Form](#). If a completed [Patient Status Form](#) is not received to authorize the continuation of treatment within 115 days, the patient is not authorized to receive the drug until a completed form is received.
2. Establish and maintain a REMS Program Website, [www.TegsediREMS.com](http://www.TegsediREMS.com). The REMS Program website must include the capability to complete prescriber certification online, the capability to enroll and manage patients online including patient authorization status, report severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis events online, and the option to print the Prescribing Information, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
3. Make the REMS Program website fully operational and all REMS materials available through the website or call center by the date Tegsedi is first commercially distributed.
4. Establish and maintain a REMS Program call center for REMS participants at 1-844-483-4736.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Tegsedi REMS Program.
6. Ensure prescribers are able to become certified in the REMS by fax and online.
7. Ensure prescribers are able to enroll patients in the REMS by fax and online.
8. Ensure pharmacies are able to become certified in the REMS by fax.
9. Ensure pharmacies are able to obtain authorization to dispense by phone or online.
10. Ensure prescribers and pharmacies are able to report adverse events suggestive of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis by contacting the REMS program by phone, online and fax, or using the [Patient Status Form](#) by online and fax.
11. Provide the [Program Overview](#), [Prescriber Training](#), [Prescriber Enrollment Form](#), [Patient Guide](#), [Patient Enrollment Form](#), [Wallet Card](#), and the Prescribing Information to prescribers who attempt to prescribe Tegsedi and are not yet certified or inquire about how to become certified.
12. Provide the [Pharmacy Enrollment Form](#) and Program Overview and the Prescribing Information to pharmacies who are contracted with Ionis Pharmaceuticals and attempt to dispense Tegsedi and are not yet certified or inquire about how to become certified.
13. Notify prescribers and pharmacies within 24 hours after they become certified in the REMS Program.
14. Provide certified prescribers access to the database of enrolled patients.

15. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
16. Establish and maintain a registry which includes a reporting and collection system for all patients to provide information on the incidence of 1) severe thrombocytopenia 2) serious bleeding with severe thrombocytopenia, and 3) glomerulonephritis.
17. Ensure that once a report suggestive of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, or glomerulonephritis is received, Ionis Pharmaceuticals follows-up with the healthcare provider to obtain all required data for the registry.

**To ensure REMS participants' compliance with the REMS Program, Ionis Pharmaceuticals must:**

18. Ensure the [Patient Status Form](#) is received for each patient. If the form is not received within every 95 calendar days of the date of the first dispense of TEGSEDI, Ionis Pharmaceuticals must contact the prescriber to obtain the form. If the form is not received within every 115 calendar days, the patient is not authorized to receive the drug until the form is received.
19. Verify annually that the certified pharmacy's designated authorized representative remains the same. If different, the pharmacy must re-certify with a new authorized representative.
20. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to, records of: Tegsedi distribution and dispensing; prescriber and pharmacy certification; patient enrollment; and audits of REMS participants. These records must be readily available for FDA inspections.
21. Establish a plan for addressing noncompliance with REMS Program requirements.
22. Monitor prescribers and pharmacies on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
23. Audit pharmacies and wholesalers-distributors no later than 90 calendar days after they become certified/authorized to distribute the drug, and annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
24. Take reasonable steps to improve implementation of and compliance with the requirements of the Tegsedi REMS Program based on monitoring and evaluation of the Tegsedi REMS Program.

## **IV. REMS Assessment Timetable**

Ionis Pharmaceuticals must submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (10/05/2018). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Ionis Pharmaceuticals must submit each assessment so that it will be received by the FDA on or before the due date.

## **V. REMS Materials**

The following materials are part of the Tegsedi REMS:

### **Enrollment Forms**

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Pharmacy Enrollment Form](#)

### **Training and Educational Materials**

Prescriber:

4. [Program Overview](#)
5. [Prescriber Training](#)
6. [Prescriber Knowledge Assessment](#)

Patient:

7. [Patient Guide](#)
8. [Wallet Card](#)

Pharmacy:

9. [Program Overview](#)

### **Patient Care Forms**

10. [Patient Status Form](#)

### **Other Materials**

11. [REMS Program website](#)



## TEGSEDI™ REMS Prescriber 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.

### Instructions:

- 1) Review the TEGSEDI Prescribing Information (PI), the *Program Overview*, and the *Prescriber Training*.
- 2) Complete the *Prescriber Knowledge Assessment* and this *Prescriber Enrollment Form*.
- 3) Submit the completed *Prescriber Knowledge Assessment* and this enrollment form:
  - Online at [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com)
  - Or Fax: 1-855-4TEGREMS (1-855-483-4736).

Please complete all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify you of successful certification.

### PRESCRIBER AGREEMENT

By signing below, I agree TEGSEDI is only available through the REMS and I must comply with the following REMS requirements:

#### I have:

- Reviewed the Prescribing Information, *REMS Program Overview* and the *Prescriber Training*
- Successfully completed the *Prescriber Knowledge Assessment* and submitted it to the REMS

#### Before treatment initiation (first dose) I must:

- Counsel the patient on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis and the need to have their platelets 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, estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and the appropriateness of initiating treatment
- 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 I must:

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

#### During treatment every 2 weeks I must:

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

#### During treatment every 90 days I must:

- 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*

#### For eight weeks after treatment is discontinued, I must:

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

#### Eight weeks after treatment is discontinued, I must:

- Assess the patient's platelet count and signs and symptoms of thrombocytopenia. Document and submit to the REMS 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 using the *Patient Status Form*

#### At all times, I must:

- Report events of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis by contacting the REMS by phone, online, and fax or by using the *Patient Status Form* online and by fax
- Report treatment discontinuation or transfer of care to the REMS using the *Patient Status Form*

#### I understand and acknowledge that:

- I will only be able to prescribe TEGSEDI if certified in the REMS
- I am responsible for safeguarding my credentials for the REMS website. I will not share my credentials for the REMS website or allow others to sign into the website using my credentials
- I will allow Ionis Pharmaceuticals and its agents to contact me via phone, mail, fax, or email to support administration of the REMS
- I understand that if I fail to maintain compliance with the requirements of the TEGSEDI REMS, I may no longer be able to prescribe TEGSEDI

# TEGSEDI™ REMS Prescriber Enrollment Form

PRESCRIBER INFORMATION			(Fields marked * are required)
First Name*:	Middle Initial:	Last Name*:	
National Provider Identifier # (NPI)*:			
Credentials*: <input type="checkbox"/> MD <input type="checkbox"/> DO <input type="checkbox"/> NP <input type="checkbox"/> PA <input type="checkbox"/> Other (please specify)			
Specialty*: <input type="checkbox"/> Neurology <input type="checkbox"/> Hematology <input type="checkbox"/> Other (please specify):			
Practice type*: <input type="checkbox"/> Solo Private Practice <input type="checkbox"/> Group Private Practice <input type="checkbox"/> Academic/Hospital-Affiliated Practice <input type="checkbox"/> Government Institution <input type="checkbox"/> Other (please specify):			
Practice/Facility Name:			
Address Line 1*:			
Address Line 2:			
City*:		State*:	Zip Code*:
Phone*:	Fax*:		Email*:
Preferred method of contact*: <input type="checkbox"/> Phone <input type="checkbox"/> Fax <input type="checkbox"/> Email			

OFFICE CONTACT		
First Name:	Last Name:	
Phone: <input type="checkbox"/> Same as above	Fax: <input type="checkbox"/> Same as above	Email (required if Office Contact is provided):

*To provide additional Office Contacts please contact the TEGSEDI REMS Coordinating Center at 1-844-4TEGREMS (1-844-483-4736).*

Prescriber Signature*: 	Date*:
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**Report serious side effects of TEGSEDI to the REMS at 1-833-MI AKCEA (1-833-642-5232) and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.**

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



# TEGSEDI™ REMS

## Patient Enrollment Form

### PRESCRIBER AGREEMENT

By signing below, I attest that prior to prescribing TEGSEDI:

- I have assessed the patient's platelet count, estimated glomerular filtration rate, urinalysis, and urine protein to creatinine ratio and determined that it is appropriate for this patient to receive TEGSEDI
- I have counseled my patient on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis and the need for mandatory ongoing platelet and renal function monitoring
- I have counseled my patient with the *Patient Guide* and the *Wallet Card*

Prescriber Signature\*:

X

Date\*:

### PATIENT AGREEMENT

By signing below, I understand and I acknowledge that:

Before my treatment begins, I will:

- Review the *Patient Guide* and *Wallet Card*
- Enroll in the REMS by completing the *Patient Enrollment Form* with my healthcare provider. Enrollment information will be provided to the REMS
- Get a blood test to check my platelet count and a blood test and urine test to check my kidneys
- Receive counseling from my healthcare provider on the risk of serious bleeding, the risk of kidney inflammation (glomerulonephritis) and kidney failure, and the need to complete the appropriate laboratory testing using the *Patient Guide* and *Wallet Card*

During treatment every week or more frequently as directed by my healthcare provider, I will:

- Get a blood test to check my platelet count

During treatment every two weeks, I will:

- Get a blood test and urine test to check my kidneys

If my healthcare provider has me stop taking TEGSEDI, I will:

- Continue to get my blood and urine tested every 1-2 weeks or more frequently as directed by my healthcare provider, for 8 more weeks

I understand that:

- I will contact my healthcare provider or go to the emergency room if I have any side effects, reactions, or symptoms after receiving TEGSEDI
- I have received, read, and understand that I will carry the *Wallet Card* with me at all times
- I have received, read, and understand the *Patient Guide* that my healthcare provider has given me
- TEGSEDI can cause serious side effects. It can cause low platelet counts that may lead to serious bleeding that could lead to death. It can also cause kidney inflammation and kidney failure that needs dialysis. These complications can be identified through lab testing and awareness of side effects, reactions, or symptoms. My healthcare provider has reviewed with me the risks of treatment with TEGSEDI
- In order to receive TEGSEDI, I am required to be enrolled in the REMS, and my information will be stored in a database of all patients who receive TEGSEDI in the United States
- Ionis Pharmaceuticals and its agents, including trusted vendors, may contact me via phone, mail, fax, or email to support administration of the REMS
- Ionis Pharmaceuticals and its agents, including trusted vendors, may use, disclose, and share my personal health information for the purpose of the operations of the REMS, including enrolling me into the REMS and administering the REMS, coordinating the dispensing of TEGSEDI, and releasing and disclosing my personal health information to the Food and Drug Administration (FDA), as necessary, and as otherwise required by law

\*Indicates required field

Printed Patient or Legal Guardian First and Last Name:

Patient or Legal Guardian Signature\*:

X

Date\*:

**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

TEGSEDI is a trademark of Ionis Pharmaceuticals, Inc.

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Reference ID: 4330796





## TEGSEDI™ REMS Pharmacy Enrollment Form

### Instructions:

TEGSEDI (inotersen) 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.

If you have questions, please contact the TEGSEDI REMS at 844-4TEG-REMS (844-483-4736).

Please fax this completed form to the TEGSEDI REMS at 1-855-4TEGREMS (855-483-4736).

### AUTHORIZED PHARMACY REPRESENTATIVE RESPONSIBILITIES

I am the authorized representative designated by my pharmacy to coordinate the activities of the TEGSEDI REMS. By signing this form, I agree, on behalf of myself and my pharmacy, to comply with the following REMS requirements:

- I will oversee implementation of and ensure my pharmacy's compliance with the TEGSEDI REMS requirements
- I have reviewed the *Program Overview* and will ensure that all relevant staff involved in the dispensing of TEGSEDI are trained on the TEGSEDI REMS requirements using the *Program Overview*, and that a record of training is maintained
- I will enroll in the TEGSEDI REMS by completing the *Pharmacy Enrollment Form* and submitting it to the TEGSEDI REMS
- This pharmacy will establish processes and procedures to dispense no more than a 30-day supply of TEGSEDI
- I will ensure that, prior to dispensing TEGSEDI, this pharmacy will verify that the prescriber is certified and the patient is enrolled and is authorized to receive TEGSEDI by contacting the TEGSEDI REMS
- This pharmacy will dispense no more than a 30-day supply of TEGSEDI
- This pharmacy will have a new authorized representative enroll in the REMS by completing the *Pharmacy Enrollment Form* and submitting it to the REMS if the authorized representative changes
- This pharmacy will establish processes and procedures to ensure that adverse events of severe thrombocytopenia, serious bleeding with severe thrombocytopenia and glomerulonephritis are reported to the REMS
- This pharmacy will report severe thrombocytopenia, serious bleeding with severe thrombocytopenia and glomerulonephritis to the REMS
- I will ensure that this pharmacy will not distribute, transfer, loan, or sell TEGSEDI
- This pharmacy will maintain and make available appropriate documentation reflecting the staff's completion of REMS training and all processes and procedures are in place and being followed
- I understand that non-compliance with the requirements of the TEGSEDI REMS will result in decertification of my pharmacy and termination of authorization to dispense TEGSEDI
- This pharmacy will comply with audits by Ionis Pharmaceuticals, the US Food and Drug Administration (FDA), or a designated third party acting on behalf of Ionis Pharmaceuticals or FDA to ensure compliance with the TEGSEDI REMS

### PHARMACY INFORMATION (\*required)

Pharmacy Name\*:

Pharmacy Address\*:

City\*:

State\*:

Zip Code\*:

Type of Pharmacy\*:  Specialty  Long-term care  Hospital pharmacy  Other (please specify):

Pharmacy Identifier\*  
(at least one required)

NPI:

NCPDP:

DEA:

### PHARMACY Ship to Address, if different than above

Pharmacy Address Line #1:

Pharmacy Address Line #2:

City:

State:

Zip Code:



AUTHORIZED PHARMACY REPRESENTATIVE INFORMATION (*required)		
First Name*:	Last Name*:	MI:
Telephone Number*:	Alternate Telephone Number:	Office Fax*:
Email*:	Preferred method of communication: <input type="checkbox"/> Email <input type="checkbox"/> Fax <input type="checkbox"/> Phone	
Authorized Pharmacy Representative Signature*: <b>X</b>	Date*:	

By completing and submitting this form and receiving enrollment confirmation, your pharmacy will be certified in the TEGSEDI REMS. You will receive confirmation of your enrollment via your preferred method of communication.

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

# TEGSEDI™ REMS Program Overview (Risk Evaluation and Mitigation Strategy)

This overview describes the requirements of the TEGSEDI (inotersen) REMS and the responsibilities of prescribers, pharmacies and patients.

If you have any questions regarding the TEGSEDI REMS, please visit [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) or call 1-844-4TEGREMS (1-844-483-4736).



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## 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 due to severe thrombocytopenia and the risk of glomerulonephritis, TEGSEDI is available only under a restricted program called the TEGSEDI REMS.**

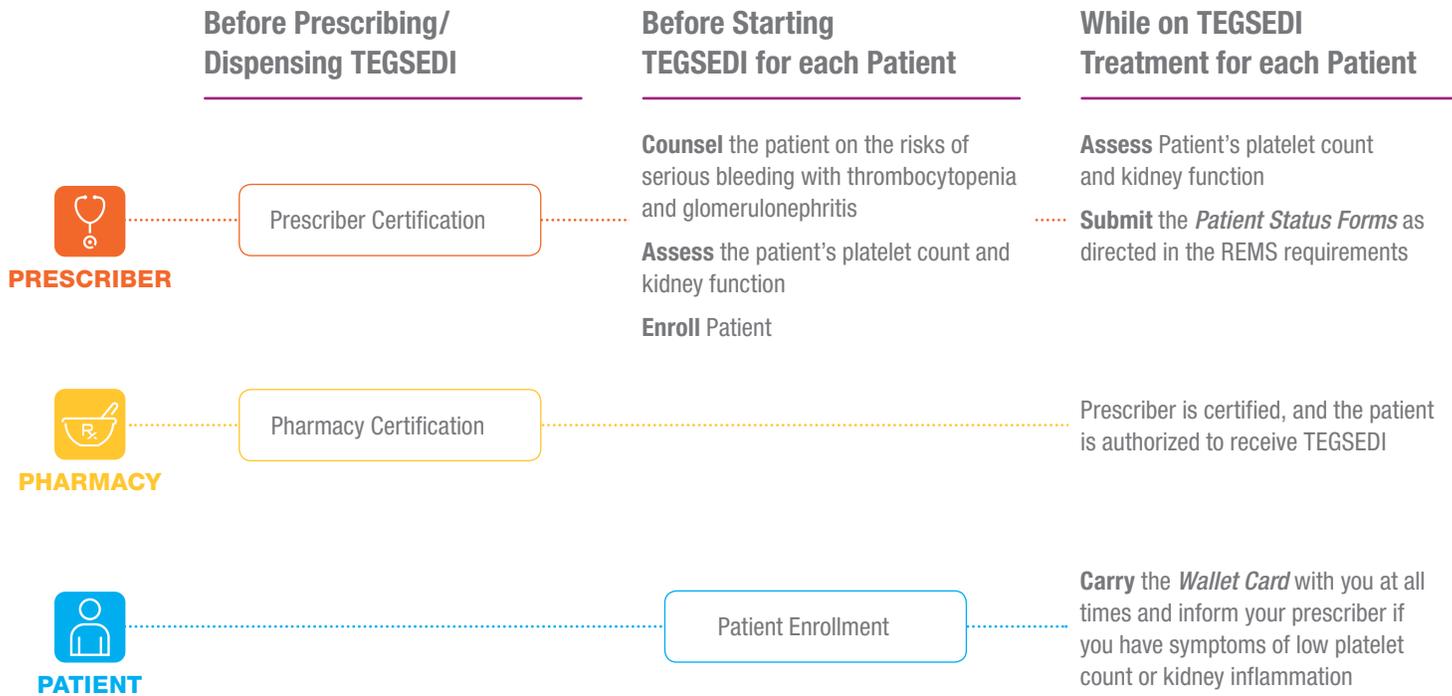
TEGSEDI may cause serious bleeding due to severe thrombocytopenia. The signs and symptoms of thrombocytopenia may include:

- 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

TEGSEDI may cause glomerulonephritis. 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

## How does the TEGSEDI REMS work?



## What are the Requirements of the TEGSEDI REMS?

- In order to receive TEGSEDI, prescribers, pharmacies, and patients must comply with the requirements of the TEGSEDI REMS

### To prescribe TEGSEDI:



- Become certified** by completing a one-time certification process
- Assess** the patient's platelet count and kidney function
- As you start patients on TEGSEDI, **counsel** and **enroll** them into the TEGSEDI REMS
- Perform** ongoing assessments of platelet counts and kidney function
- Document and Submit** a *Patient Status Form* during treatment, at the time of treatment discontinuation and 8 weeks after treatment discontinuation

### To dispense TEGSEDI\*:



- Designate an authorized representative, become certified, and recertify** if there is a change in the authorized representative
- Train** staff and **comply** with REMS requirements
- Before dispensing TEGSEDI, **verify** prescriber is certified and patient is authorized to receive TEGSEDI

### To receive TEGSEDI:



- Understand** the risks associated with TEGSEDI
- Enroll** in the REMS by completing the *Patient Enrollment Form* with your healthcare provider
- Get** a blood test and a urine test during treatment and after treatment discontinuation

\*TEGSEDI is not available to all pharmacies. If you have any questions about the REMS or how to obtain TEGSEDI, call 1-844-483-4736.



## Prescriber Requirements

### Become Certified (One-time)

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#### Before prescribing TEGSEDI:

1. **Review** the following educational materials on TEGSEDI to understand the risks of serious bleeding with thrombocytopenia and glomerulonephritis, and the TEGSEDI REMS:
  - Prescribing Information
  - Prescriber Training
  - REMS Program Overview
2. **Complete** and **submit** the following to become certified:
  - Prescriber Knowledge Assessment
  - Prescriber Enrollment Form
3. Once completed, the TEGSEDI REMS will notify you that you are certified to prescribe TEGSEDI

### Enroll Patients

---

#### Before starting each patient on TEGSEDI:

1. **Counsel** your patient about the risks associated with TEGSEDI, including serious bleeding with thrombocytopenia and glomerulonephritis and share the resources below:
  - Patient Guide
  - Wallet Card
2. **Assess** the patient's platelet count and kidney function for appropriateness of initiating treatment
3. **Submit** a completed *Patient Enrollment Form* to the TEGSEDI REMS. Provide a copy of the form to the patient

### At All Times

---

#### Once your patient is on TEGSEDI:

1. **Report** any events of severe thrombocytopenia, serious bleeding with thrombocytopenia, and glomerulonephritis to the REMS Program
2. **Assess** the patient's appropriateness for continuing treatment by monitoring their platelet count and kidney function
3. **Submit** the *Patient Status Form*\* during treatment, at the time of treatment discontinuation and at 8 weeks after treatment discontinuation
4. **Inform** the TEGSEDI REMS if a patient is no longer under your care or has discontinued TEGSEDI

\*The REMS will send a reminder to the certified prescriber of record when the *Patient Status Form* is due. Completed forms should be submitted to the TEGSEDI REMS online at [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) or via fax to 1-855-483-4736. *Patient Status Forms* may be submitted by certified Prescribers online or via fax.



## Pharmacy Requirements

### Become Certified

---

#### Before Dispensing TEGSEDI:

1. **Designate** an authorized representative for the pharmacy to carry out the certification process. He or she will need to review the *REMS Program Overview* and will oversee implementation and ensure compliance with the TEGSEDI REMS requirements
2. Have the authorized representative **complete and submit** the *Pharmacy Enrollment Form* by fax
  - Once this step is completed, the TEGSEDI REMS will notify you that you are certified to dispense TEGSEDI
3. Have the authorized representative ensure that all relevant staff involved in dispensing of TEGSEDI are trained on the TEGSEDI REMS requirements using the *Program Overview*, and that a record of the training is maintained by the pharmacy
4. Establish processes and procedures to dispense no more than a 30-day supply
5. Establish processes and procedures to report severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis events to the REMS

### Ensure Compliance with REMS Requirements

---

#### When Dispensing TEGSEDI:

1. Before dispensing TEGSEDI, **verify** that the prescriber is certified and the patient is authorized to receive TEGSEDI by accessing the TEGSEDI REMS Portal or by calling the TEGSEDI REMS
2. **Report** severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis events to the REMS
3. **Maintain** records that all REMS processes and procedures are in place and are being followed
4. **Recertify** in the TEGSEDI REMS if a new authorized representative is designated by completing and submitting the *Pharmacy Enrollment Form*

TEGSEDI is not available to all pharmacies. If you have questions about the REMS or how to obtain TEGSEDI, call 1-844-483-4736.



## Patient Requirements

### Enroll and Get Blood and Urine Testing

#### Before starting TEGSEDI:

1. Discuss with your doctor and understand:
  - The risks associated with TEGSEDI, including serious bleeding and kidney inflammation
  - The need to complete the appropriate lab testing
2. Receive and read the:
  - *Patient Guide*
  - *Wallet Card*
3. Complete the *Patient Enrollment Form* with your doctor

### Complete Ongoing Testing as Directed by Prescriber

#### After starting TEGSEDI:

1. Carry the *Wallet Card* with you at all times and Inform your healthcare provider about this treatment
2. Inform your healthcare provider if you have any signs and symptoms of low platelet count or kidney inflammation
3. Get the appropriate lab testing during treatment and after discontinuation

## TEGSEDI REMS Resources



### PRESCRIBER



### PHARMACY



### PATIENT

#### Before Prescribing/ Dispensing TEGSEDI

- Prescribing Information
- *Prescriber Training*
- *Program Overview*
- *Prescriber Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient Enrollment Form*

- *Program Overview*
- *Pharmacy Enrollment Form*

#### Before Starting TEGSEDI for each Patient

- *Patient Enrollment Form*
- *Wallet Card*
- *Patient Guide*

#### While on TEGSEDI Treatment and 60 days post TEGSEDI Discontinuation

- *Patient Status Form*

TEGSEDI is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Please see the Prescribing Information for more information.





Visit [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com) or call the TEGSEDI REMS at 1-844-483-4736 for any questions about the TEGSEDI REMS.

Please see the Prescribing Information for more information.

**Website:** [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com)

**Phone:** 1-844-483-4736

**Fax:** 1-855-483-4736

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## 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  $100 \times 10^9/L$
- 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 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 periods (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 a 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  $50 \times 10^9/L$ ), 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 to further support long-term safety and safe use of TEGSEDI



## 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*

#### 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 serious side effects of TEGSEDI to the REMS at 1-833-MI AKCEA (1-833-642-5232) and/or the FDA at [www.fda.gov/medwatch](http://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*

For more information about the TEGSEDI REMS, please visit [www.TEGSEDIrems.com](http://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.



TEGSEDI™ REMS

## Prescriber Knowledge Assessment

Prescriber Name:	Date:
Prescriber NPI:	
Prescriber Email:	Prescriber Phone:

**To become a certified prescriber in the TEGSEDI REMS, you have 3 attempts to answer all questions correctly.**

- Review the Prescribing Information, *Prescriber Training* and *Program Overview*.
- Complete this *Prescriber Knowledge Assessment* and the *Prescriber Enrollment Form*.
- Fax your responses to the 9 *Prescriber Knowledge Assessment* questions and the *Prescriber Enrollment Form* to 1-855-4TEGREMS (855-483-4736).
- You will be notified via email by the TEGSEDI REMS Program on the status of your certification within two business days of submitting. When contacted, you will receive either:
  - Confirmation of your certification in the TEGSEDI REMS Program
 Or
  - Instructions on how to retake the *Prescriber Knowledge Assessment*. You will be given the opportunity to retake the test by providing answers for only the questions you answered incorrectly. If you do not answer all 9 questions correctly in 3 attempts, you will be instructed to re-review the materials and once reviewed, you will have another 3 attempts to complete the test.
  - If the *Prescriber Knowledge Assessment* is not successfully completed after 6 attempts, you will be contacted by the TEGSEDI REMS via telephone and informed that a representative from Ionis Pharmaceuticals will reach out to discuss your certification.



# TEGSEDI™ REMS Prescriber Knowledge Assessment

## Questions 1-9

### Question 1 (check one)

To certify in the TEGSEDI REMS Program I must:

- A. Review the Prescribing Information
- B. Review the *Prescriber Training*
- C. Successfully complete the *Prescriber Knowledge Assessment*
- D. Enroll in the TEGSEDI REMS by completing and signing the *Prescriber Enrollment Form*
- E. All of the above

### Question 2

TEGSEDI can cause severe thrombocytopenia that may occur suddenly

- True
- False

### Question 3 (check one)

Before TEGSEDI treatment (first dose), I must:

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

### Question 4

Testing and monitoring for severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis is not a requirement of the TEGSEDI REMS

- True
- False

### Question 5

At all times during treatment with TEGSEDI a prescriber must:

Report events of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis to the REMS Program and report treatment discontinuation or transfer of care to the REMS Program

- True
- False

### Question 6

Match each lab value to the monitoring frequency as described in the TEGSEDI Prescribing Information (PI) during treatment:

- |                        |                             |                             |                             |                             |
|------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Platelets (check one)  | <input type="checkbox"/> A. | <input type="checkbox"/> B. | <input type="checkbox"/> C. | <input type="checkbox"/> D. |
| eGFR (check one)       | <input type="checkbox"/> A. | <input type="checkbox"/> B. | <input type="checkbox"/> C. | <input type="checkbox"/> D. |
| Urinalysis (check one) | <input type="checkbox"/> A. | <input type="checkbox"/> B. | <input type="checkbox"/> C. | <input type="checkbox"/> D. |
| UPCR (check one)       | <input type="checkbox"/> A. | <input type="checkbox"/> B. | <input type="checkbox"/> C. | <input type="checkbox"/> D. |

- A. Do not need monitoring
- B. Weekly or more frequently as described in the PI.
- C. Every 2 weeks
- D. Every 3 months

### Question 7 (check one)

If a platelet measurement is uninterpretable, I should hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample

- True
- False

### Question 8 (check one)

I should complete and submit a *Patient Status Form* to the REMS Program:

- A. Once annually
- B. Every 90 days during treatment
- C. Eight weeks following discontinuation of TEGSEDI
- D. Every 2 months during treatment
- E. Both B & C above

### Question 9 (check one)

TEGSEDI can cause glomerulonephritis

- True
- False

## 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



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## 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):**

---

**Prescriber phone #:**

**Reference ID: 4330796**

---



## 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).

Reference ID: 4330796


**TEGSEDI™ REMS**  
**Patient Status Form**

**This form must be regularly completed for all patients treated with TEGSEDI as follows:**

- Every 90 days following the first dispense of TEGSEDI treatment
- In the event of TEGSEDI treatment discontinuation
- At 8 weeks following notification of a discontinuation of TEGSEDI treatment

Submit the completed form:

- Online at [www.TEGSEDIrems.com](http://www.TEGSEDIrems.com)
- Or Fax: 1-855-4TEGREMS (855-483-4736)

Following a treatment initiation, certified prescribers must assess each patient's platelet count and renal function [estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR)] and appropriateness of continuing treatment as follows:

- Platelet count: Every week or more frequently as described in the Prescribing Information
- Renal function: Every 2 weeks

**After a treatment discontinuation, the patient's platelet count and renal function must continue to be monitored for 8 weeks as follows:**

- **Platelet count: Every week**
- **Renal function: Every two weeks**

*NOTE: The completion of laboratory tests and the submission of this form are done at different intervals.*

PRESCRIBER INFORMATION (*required)			
National Provider Identifier #*:			
First Name*:		Last Name*:	
Practice/Facility Name:			
Address Line 1:			
Address Line 2:			
City:		State:	Zip Code:
Phone:	Fax:		Email:

PATIENT INFORMATION (PLEASE PRINT) (*required)		
First Name*:	Last Name*:	Birthdate* (MM/DD/YYYY):
Address Line 1*:		
Address Line 2:		
City*:	State*:	Zip Code*:

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



## TEGSEDI™ REMS Patient Status Form

1.	I have assessed the patient's signs and symptoms and reviewed the patient's required laboratory tests [platelet count, estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR)] during this reporting period.	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.	Patient status:	
	2a. The patient is continuing therapy with TEGSEDI:	<input type="checkbox"/> Yes <input type="checkbox"/> No
	2b. If YES, the patient is continuing therapy with TEGSEDI, I have assessed the patient's signs and symptoms and required laboratory tests during this reporting period and confirm this patient is appropriate to continue to receive TEGSEDI:	<input type="checkbox"/> Yes <input type="checkbox"/> No
	2c. If NO, the patient has discontinued therapy with TEGSEDI, please indicate the reason(s):	
	<input type="checkbox"/> Thrombocytopenia <input type="checkbox"/> Death <input type="checkbox"/> Glomerulonephritis <input type="checkbox"/> Other _____	
	<b>Please report all Adverse Events to Ionis Pharmaceuticals at 1-833-642-5232</b>	
3.	Did the patient experience serious bleeding with severe thrombocytopenia (platelet count $<50 \times 10^9/L$ )?	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.	If the answer to question 3 is YES, did the patient have a platelet measurement within 2 weeks of the start of bleeding?	<input type="checkbox"/> Yes <input type="checkbox"/> No
5.	Was the patient diagnosed with glomerulonephritis?	<input type="checkbox"/> Yes <input type="checkbox"/> No
6.	Is the above-named patient still under the care of the prescriber identified above?	<input type="checkbox"/> Yes <input type="checkbox"/> No
7.	If the answer to question 6 is NO, please indicate the name of the prescriber now responsible for this patient's care:	
	Prescriber Name: _____	
	Prescriber Phone Number: _____	
	<input type="checkbox"/> Prescriber now responsible for this patient's care is unknown.	

Print Name*:	
Certified Prescriber Signature*: 	Date* (MM/DD/YYYY):

Please note: The certified prescriber of record is responsible for compliance with the TEGSEDI REMS requirements, including monitoring, evaluation, and management of each patient under his/her care. If you have questions on this information, please call 1-844-483-4736.

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

TEGSEDI REMS (Risk Evaluation and Mitigation Strategy) Program

**What is the TEGSEDI REMS?**

A REMS (Risk Evaluation and Mitigation Strategy) 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 due to severe thrombocytopenia and the risk of glomerulonephritis, TEGSEDI is available only under a restricted program called the TEGSEDI REMS.

**Prescribers**

Prescribers must be certified in TEGSEDI REMS to prescribe TEGSEDI for adult patients with polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR).

Learn about Prescriber Certification

[LEARN MORE](#)

**Pharmacies**

Pharmacies must be certified in TEGSEDI REMS to dispense TEGSEDI for adult patients with polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR).

Learn about Pharmacy Certification

[LEARN MORE](#)

**Patients**

Patients who are prescribed TEGSEDI for the treatment of polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR) must be enrolled in the TEGSEDI REMS Program.

Learn about Patient Enrollment

[LEARN MORE](#)

**TEGSEDI is not available to all pharmacies. If you have questions about TEGSEDI REMS or need help with certification or enrollment, call 1-844-483-4736. Monday-Friday, 8:00am – 8:00pm ET**

! You are encouraged to report serious side effects of TEGSEDI to the REMS at 1-833-642-5232, and/or the FDA at [www.fda.gov/mcdwatch](http://www.fda.gov/mcdwatch) or call 1-800-FDA-1088.

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TEGSEDI REMS Prescriber Enrollment

PRESCRIBING INFORMATION MEDICATION GUIDE REGISTER LOG IN

Home Prescribers Pharmacies Patients Forms & Resources

## TEGSEDI REMS Prescriber Enrollment

Prescribers must be certified in the TEGSEDI REMS Program to be able to prescribe TEGSEDI for adult patients with polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR). Because of the safety profile of TEGSEDI, patients treated with TEGSEDI should have lab monitoring prior to initiating therapy and ongoing monitoring during treatment as described in the Prescribing Information.

To become certified in the program, prescribers must complete the following steps:

- STEP 1** REVIEW the TEGSEDI Prescribing information
- STEP 2** REVIEW the Prescriber Training and REMS Program Overview
- STEP 3A** COMPLETE AND SUBMIT the following online:
  - Prescriber Knowledge Assessment
  - Prescriber Enrollment Form
- OR
- STEP 3B** VIA FAX at 855-483-4736
- STEP 4** RECEIVE notification of successful enrollment and username and password to log in to the TEGSEDI REMS Program and view your enrolled patients

### Materials for Prescribers

- Prescriber Training [PDF]
- REMS Program Overview [PDF]
- Prescriber Knowledge Assessment [PDF]
- Prescriber Enrollment Form [PDF]
- Patient Enrollment Form [PDF]
- Patient Guide [PDF]
- Patient Status Form [PDF]
- Patient Wallet Card [PDF]

Adobe® Reader® is required to view PDFs. If you do not have it installed, [download it free here.](#)

If you have questions about TEGSEDI REMS or need help with certification, call **1-844-483-4736**.  
Monday-Friday, 8:00am – 8:00pm ET



You are encouraged to report serious side effects of TEGSEDI to the REMS at 1-833-642-5232, and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.



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TEGSEDI REMS Patient Information

Below are materials that help inform patients about treatment with TEGSEDI.

**Materials for Patients**

Patient Guide [PDF]

Patient Wallet Card [PDF]

Adobe® Reader® is required to view PDFs. If you do not have it installed, [download it free here.](#)

**If you have questions about TEGSEDI REMS or need help enrolling, call 1-844-483-4736. Monday-Friday, 8:00am - 8:00pm ET**



You are encouraged to report serious side effects of TEGSEDI to the REMS at 1-833-642-5232, and/or the FDA at [www.fda.gov/mcdwatch](http://www.fda.gov/mcdwatch) or call 1-800-FDA-1088.



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PRESCRIBING INFORMATION MEDICATION GUIDE REGISTER LOG IN

Home Prescribers Pharmacies Patients Forms & Resources

## TEGSEDI REMS Enrollment Forms & Resources

Below are downloadable forms needed to support the TEGSEDI REMS Program.

Adobe Reader is required to view PDFs. If you do not have it installed, [download it free here.](#)

### Materials for Prescribers

- Prescriber Training [PDF]
- REMS Program Overview [PDF]
- Prescriber Knowledge Assessment [PDF]
- Prescriber Enrollment Form [PDF]
- Patient Enrollment Form [PDF]
- Patient Guide [PDF]
- Patient Status Form [PDF]
- Patient Wallet Card [PDF]

### Materials for Pharmacies

- REMS Program Overview [PDF]
- Pharmacy Enrollment Form [PDF]

### Materials for Patients

- Patient Guide [PDF]
- Patient Wallet Card [PDF]

If you have questions about TEGSEDI REMS or need help with certification or enrollment, call 1-844-483-4736. Monday-Friday, 8:00am - 8:00pm ET

You are encouraged to report serious side effects of TEGSEDI to the REMS at 1-833-642-5232, and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

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The screenshot shows a web browser window with the URL `tegsedirems.wpengin`. The page content is dimmed, showing a navigation menu with 'Home', 'Prescribers', 'Pharmacies', 'Patients', and 'Forms & Resources'. A modal popup is centered on the screen with the following text:

**CLOSE [X]**

By clicking "Continue" you will exit the TEGSEDI REMS website.

**CANCEL** **CONTINUE**

The background page lists 'Materials for Prescribers', 'Materials for Pharmacies', and 'Materials for Patients' with various PDF links. At the bottom, there is a contact information box and a warning icon.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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ROBERT TEMPLE  
10/05/2018