

# Risk Evaluation and Mitigation Strategy (REMS) Document

## Tegsedi (inotersen) REMS Program

### I. Administrative Information

Application Number: NDA 211172  
Application Holder: Akcea Therapeutics  
Initial REMS Approval: 10/2018  
Most Recent REMS Update: 05/2020

### 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

Akcea Therapeutics 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. <b>Review the drug's Prescribing Information.</b></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></ol> |
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	4. Enroll in the REMS by completing the <a href="#">Prescriber Enrollment Form</a> and submitting it to the REMS Program.
Before treatment initiation (first dose)	<p>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>.</p> <p>6. Provide the patient with the <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</p> <p>7. <b>Assess the patient's platelet count and appropriateness of initiating treatment.</b> Document and submit to the REMS Program using the <a href="#">Patient Enrollment Form</a>.</p> <p>8. <b>Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and appropriateness of initiating treatment.</b> Document and submit to the REMS Program using the <a href="#">Patient Enrollment Form</a>.</p> <p>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.</p>
During treatment; weekly or more frequently as described in the Prescribing Information	10. <b>Assess the patient's platelet count and appropriateness of continuing treatment.</b>
During treatment; every two weeks	11. <b>Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR) and appropriateness of continuing treatment.</b>
During treatment; every 90 days	<p>12. <b>Assess the patient's platelet count, signs and symptoms of thrombocytopenia, and appropriateness of continuing treatment.</b> Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</p> <p>13. <b>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.</b> Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</p>
After treatment discontinuation; weekly for 8 weeks or more frequently as described in the Prescribing Information	14. Assess the patient's platelet count.
After treatment discontinuation; every 2 weeks for 8 weeks	15. <b>Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR).</b>

After treatment discontinuation; at 8 weeks	<p>16. <b>Assess the patient's</b> platelet count and signs and symptoms of thrombocytopenia. Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</p> <p>17. <b>Assess the patient's estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), and signs and symptoms of renal toxicity.</b> Document and submit to the REMS Program using the <a href="#">Patient Status Form</a>.</p>
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)	<p>1. Review the <a href="#">Patient Guide</a> and <a href="#">Wallet Card</a>.</p> <p>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.</p> <p>3. Get a blood test to check platelet count and blood and urine tests to check kidneys.</p> <p>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>.</p>
During treatment; every week or more often as directed by the prescriber	<p>5. Get a blood test to check platelet count.</p>
During treatment; every two weeks	<p>6. Get blood and urine tests to check kidneys.</p>
After treatment discontinuation; weekly for 8 weeks or more often as directed by the prescriber	<p>7. Get a blood test to check platelet count.</p>
After treatment discontinuation; every 2 weeks for 8 weeks	<p>8. Get blood and urine tests to check kidneys.</p>
At all times	<p>9. Inform the prescriber of any serious bleeding or signs and symptoms of kidney inflammation.</p> <p>10. Have the <a href="#">Wallet Card</a> with you.</p> <p>11. Inform all healthcare providers about receiving this treatment.</p>

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### 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><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 day 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 30 day 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. <b>Maintain records documenting staff's</b> 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 Akcea Therapeutics or a third party acting on behalf of Akcea Therapeutics to ensure all processes and procedures are in place and are being followed.</li></ol>

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### 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>
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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 Akcea Therapeutics or a third party acting on behalf of Akcea Therapeutics to ensure all processes and procedures are in place and are being followed.</li></ol>
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Akcea Therapeutics must provide training to healthcare providers who prescribe Tegsedi. The training includes the following educational materials: [Prescriber Training](#), [Program Overview](#), [Prescriber Knowledge Assessment](#). The training must be available online and by hard copy via fax or mail.

Akcea Therapeutics 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, Akcea Therapeutics 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 Akcea Therapeutics and attempt to dispense Tegsedi and are not yet certified or inquire about how to become certified.
13. Notify prescribers and pharmacies within 48 hours after they become certified in the REMS Program.
14. Provide certified prescribers access to the database of their 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, Akcea Therapeutics follows-up with the healthcare provider to obtain all required data for the registry.

**To ensure REMS participants' compliance with the REMS Program,** Akcea Therapeutics 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, Akcea Therapeutics 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 dispense and distribute the drug, respectively, 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

Akcea Therapeutics 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. Akcea Therapeutics 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](#)