

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21172Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

1 Introduction

The following comments and the attached redlined REMS document and appended materials are based on the Agency's review of the proposed risk evaluation and mitigation strategy (REMS) for Tegsedi® (inotersen), NDA 211172, submitted by Ionis Pharmaceuticals on November 6, 2017 and amended on May 4, 2018.

The proposed indication for inotersen is the treatment of adult patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). The Applicant's proposed REMS consists of elements to assure safe use that include prescriber and pharmacy certification; safe use conditions that include patient enrollment and counseling received from the prescriber; that each patient is subject to certain monitoring; and that each patient receiving inotersen is enrolled in a registry to further support long-term safety and safe use. The REMS also includes an implementation system and a timetable for the submission of assessments.

2 Comments to the Applicant

The following comments and the attached revised REMS document and revised appended materials are based on the Agency's ongoing review of the proposed REMS for Tegsedi, submitted in NDA 211172 on November 6, 2017 and amended on May 4, 2018. We have revised the REMS document and appended REMS materials such that they are in alignment with the Agency's current draft version of the labeling. We have also made additional edits to the REMS document and re-formatted and edited the REMS materials as shown in the attached redlined versions.

To facilitate further review, we ask you to submit a response to the comments noted below in a REMS amendment within 10 business days. As part of your response, submit both a redlined Word version and a clean Word version of the REMS Document and the appended REMS materials noted below.

General comments

- We remind you that the labeling, REMS document, appended REMS materials, and REMS supporting document must all be aligned. If, after receipt of this Information Request, the Agency communicates changes to you regarding the labeling, the REMS must be aligned with those changes and the final FDA-approved version of the label.
- We have not attached a redlined version of the Program Overview. See comments below.
- We have not attached a redlined version of the Prescriber Knowledge Assessment, which remains under review. We request you do not submit a revised version of the Prescriber Knowledge Assessment until you receive further comments from the Agency.
- We have not attached a redlined version of the REMS Website. Submit redlined and clean versions of the REMS Website that align with the changes made to the REMS document and the other relevant REMS appended materials. Submission of PDF files is acceptable if Word versions are not available.
- We have not attached a redlined version of the REMS supporting document, which remains under review at this time. However, we request you address the comments noted below in your response.

REMS Document

- The Application Holder listed on the REMS document must be the same as the applicant listed on FDA Form 356h.
- Revisions have been made to the language that describes the objectives of the REMS goal.
- The language describing various REMS requirements has been clarified.
- The Patient Enrollment Form will replace the [REDACTED] (b) (4) The Patient Enrollment Form will be used to document monitoring of required baseline laboratory testing.
- The required patient monitoring schedules have been revised to align with the Agency's current draft version of the labeling, including required monitoring after discontinuation of treatment.
- Dispensing of inotersen must be limited to a 30-days supply to avoid situations where a patient could receive a refill with a greater quantity of drug at the time the Patient Status Form is due without having completed the required monitoring.
- Authorization to dispense must be linked to completion of the Patient Status Form and its submission to the REMS program by the prescriber. The authorization process will include a "grace period" during which a 30-days supply may be dispensed while receipt of a completed Patient Status Form from the prescriber is pending.
- Wholesalers-Distributors must be audited on a schedule similar to that for pharmacies.

Appended REMS Materials

1. Program Overview

- We are in agreement with describing the requirements of the REMS and the responsibilities of each relevant stakeholder including prescribers, pharmacies, and patients in the Program Overview. However, the Program Overview should only provide a high level overview of the REMS program without details that are addressed in other REMS materials. We request you revise and streamline the content as much as possible to avoid message fatigue, and resubmit. You may refer to a recently approved program, such as the Palynziq REMS Program Overview, accessible at: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Palynziq_2018_05_24_REMS_Program_Overview.pdf

2. Prescriber Training Guide

- See the attached redlined version of the Prescriber Training Guide. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

3. Prescriber Enrollment Form

- See the attached redlined version of the Prescriber Enrollment Form. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

4. Pharmacy Enrollment Form

- See the attached redlined version of the Pharmacy Enrollment Form.

5. Patient Enrollment Form

- See the attached redlined version of the Patient Enrollment Form. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

6. Patient Guide

- See the attached redlined version of the Patient Guide. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

7. Patient Status Form

- See the attached redlined version of the Patient Status Form. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

8. Patient Wallet Card

- See the attached redlined version of the Patient Wallet Card. The acceptability of the proposed changes will be dependent upon the final version of the FDA-approved labeling. Should this align with the final labeling it is acceptable, however, the labeling remains under review at this time.

REMS supporting document

- The REMS supporting document states that dispensing of inotersen will be limited to a small number of contracted specialty pharmacies that will be certified. How will inpatient facilities (including, but not limited to hospitals and long-term care facilities) and integrated healthcare systems such as the Veterans Health Administration have the ability to become certified pharmacies? If not, please address how patients in those settings will obtain inotersen in order to ensure appropriate access.

39 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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.

/s/

ROBERT G PRATT
09/04/2018

DONELLA A FITZGERALD
09/05/2018

JAMIE C WILKINS PARKER
09/05/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211172
PDUFA Goal Date	July 6, 2018
OSE RCM #	2017-2309
Reviewer Name(s)	Erin M. South, PharmD Anahita Tavakoli, MA
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	April 20, 2018
Subject	Interim Comments for the Proposed REMS for Tegsedi
Established Name	Inotersen
Trade Name	Tegsedi
Name of Applicant	Ionis Pharmaceuticals, Inc.
Applicant's Proposed	Antisense oligonucleotide inhibitor of human transthyretin (TTR)
Therapeutic Class	protein synthesis
Formulation(s)	284 mg inotersen (300 mg sodium salt)/1.5 mL in a single-dose, prefilled syringe
Dosing Regimen	<div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> <div style="background-color: #cccccc; padding: 2px;">doses should be administered</div> once every week <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div>

1 Introduction

The following comments and the attached redlined REMS document are based on the Agency's review of the proposed REMS for Tegsedi (inotersen), submitted with New Drug Application (NDA) 211172 on November 6, 2017. Tegsedi's proposed indication is the treatment of adult patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), [REDACTED] (b) (4)

[REDACTED] This application is under review in the Division of Neurology Products (DNP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Tegsedi outweigh the risk of serious bleeding due to severe thrombocytopenia and the risk of glomerulonephritis.

DRISK and DNP agree that a REMS with ETASU A (prescriber certification), B (pharmacy certification), D (safe use conditions), E (monitoring), and F (Registry) is necessary for the benefits of Tegsedi to outweigh its risks.

2 Comments to the Applicant

The following comments and the attached revised clean Word REMS document are based on the Agency's review of the proposed REMS for Tegsedi, submitted with NDA 211172 on November 6, 2017. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and submit a complete REMS amendment within 14 calendar days, by close of business (COB) May 4, 2018. Review of the REMS document, supporting document, and appended materials is ongoing. Therefore, these comments should not be considered final.

General Comments: As discussed during the March 22, 2018 teleconference, the Agency agrees that a REMS is necessary for Tegsedi, however, we do not agree with the REMS requirements, as proposed.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED] The REMS requirements should include the following:

- Prescriber certification
- Pharmacy certification
- Safe-use conditions, including:
 - Patient education and enrollment
- Monitoring
- Registry

To align with the Agency's current thinking, the following global changes should be applied to all appended materials.

- The cover page of each appended material should contain the phrase "TEGSEDI REMS" before the name of the material so the material is identifiable.
- Using the term (b) (4) as part of the name of the REMS is no longer necessary. For example, change the *TEGSEDI REMS (b) (4) Prescriber Enrollment Form* to the *TEGSEDI REMS Prescriber Enrollment Form*.
- The Agency's current thinking has changed regarding referencing the titles of REMS materials within the content of REMS materials. Repeating the prefix "TEGSEDI REMS" when referencing various materials within the content of the material is not necessary because it is redundant and decreases readability. For example, within the *Prescriber Guide* you may refer to the *Prescriber Enrollment Form*.
- Except for the REMS document, capitalize TEGSEDI for consistency throughout all REMS materials.
- Throughout REMS materials, you refer relevant stakeholder to the (b) (4) and REMS Coordinating Center. For consistency, use REMS Coordinating Center.

The recommendations provided here are based on the current proposed labeling. However, all final versions of REMS materials must be revised to be consistent with the final FDA-approved labeling.

REMS Document: Significant revisions to the REMS document are necessary to be acceptable. The attached revised clean Word version of the REMS document has been updated to conform to the new REMS document template, per the *Format and Content of a REMS Document Guidance for Industry* released in October 2017 and available at <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf>. The goals have been revised to reflect changes in the REMS requirements. Internal clearance of the REMS document is ongoing; therefore, this should not be considered final.

REMS Appended Materials:

TEGSEDI REMS Program Overview

Create an overview that describes the requirements of the Tegsedi REMS and the responsibilities of each relevant stakeholder, including prescribers, pharmacies, and patients. Limit the number of pages to a maximum of five.

The *TEGSEDI REMS Overview* should include a cover page and Table of Contents and can include the following subheadings:

- What is the TEGSEDI REMS?
- How does the TEGSEDI REMS work?
- What are the requirements of the TEGSEDI REMS?
 - Prescriber Requirements
 - Pharmacy Requirements
 - Patient Requirements

By way of example, we recommend you review the FDA-approved *LEMTRADA REMS Program Overview*, which is available in the public domain via the following link:

https://www.accessdata.fda.gov/drugsatfda_docs/rems/Lemtrada_2016-04-05_Program_Overview.pdf

TEGSEDI REMS Prescriber Guide

Change the name of this material to the *TEGSEDI REMS Prescriber Training*. To be acceptable, this material requires additional changes beyond those needed to align with the global comments outlined above. The Tegsedi indication should align with the final approved labeling and the *Prescriber Training* content (e.g., REMS goals) should be updated to align with the attached revised REMS document.

By way of example, we recommend you review the *Aveed REMS Education Program for Healthcare Providers*, available via the below link; however, with one notable exception, we recommend the *Knowledge Assessment for Prescribers* not be included in the *Prescriber Training*. See additional comments below. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Aveed_2016-12-09_Education_Program_for_Healthcare_Providers_with_Knowledge_Assessment.pdf

TEGSEDI REMS Knowledge Assessment for Prescribers

It is necessary to create this tool, which is intended to further ensure completion of prescriber training and document prescriber understanding of the REMS risks and program requirements. The *Knowledge Assessment for Prescribers* should be a standalone REMS appended material. It should consist of no more than 8-10 questions and the content should align with the risks the REMS is to mitigate. The printed version of the *Knowledge Assessment for Prescribers* should include an answer sheet with instructions detailing where to fax or email the form. Further, this form should indicate the prescriber's next steps or what prescribers can expect after submitting the form.

Prescribers must successfully complete the *Knowledge Assessment* to activate their certification in the Tegsedi REMS. By way of example, refer to the *Knowledge Assessment* included in the LEMTRADA REMS and available via the following link:

https://www.accessdata.fda.gov/drugsatfda_docs/rems/Lemtrada_2016-04-05_Knowledge_Assessment.pdf

Details that support the utilization of the *Knowledge Assessment* should be added to the REMS supporting document, and we recommend you incorporate the following:

Knowledge Assessment Attempts

- Prescribers may attempt to successfully complete the *Knowledge Assessment* (manual or web-based) up to three times. If a score of 100% is not achieved after three

attempts, the PI and the *Prescriber Training* must be reviewed again before retaking the *Knowledge Assessment*.

- Having performed the training again, three additional unsuccessful attempts at the *Knowledge Assessment* are permitted before the prescriber is determined to be ineligible to enroll.
- Ineligible prescribers, based on a total of six unsuccessful attempts to complete the *Knowledge Assessment*, will be contacted by the Tegsedi REMS and informed that they may request to have their ineligible status removed by agreeing to be contacted by a representative of Ionis.
- Ineligible prescribers who have requested to have their ineligible status removed will be contacted by a representative of Ionis, who will determine whether to remove the ineligible status on a case-by-case basis.
- Prescribers who have had their ineligible status removed can become certified to prescribe Tegsedi by reviewing the PI and *Prescriber Training* and successfully completing the *Knowledge Assessment*.

TEGSEDI REMS Pharmacy Enrollment Form

To be acceptable, this material requires additional changes beyond aligning with the above global comments. The authorized pharmacy representative should be required to review the *Program Overview* before completing the *Pharmacy Enrollment Form*. Revise content and improve formatting. By way of example, we recommend you review the *SILIQ REMS Pharmacy Enrollment Form*, available via the following link:

https://www.accessdata.fda.gov/drugsatfda_docs/rem/siliq_2018_01_26_Pharmacy_Enrollment_Form.pdf

(b) (4)

TEGSEDI REMS Website

Create a REMS-specific website. Submit all screen shots and actual layout in both a PDF (to show the appropriate formatting and design) and Word version for review.

We recommend that you include a prominent link on the product website's homepage www.tegsedi.com for REMS materials. This link should be called "REMS" and direct users to a separate webpage that describes the REMS program and includes only approved REMS materials.

All REMS materials on the REMS website (i.e., *Guides, Forms, Program Overview*) should be downloadable from the REMS website and should be made available for the duration of the REMS.

The REMS-related webpage(s) should not be a means to promote TEGSEDI or any other Ionis product. Ensure the REMS website is independent of the link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the www.tegsedi.com website. Furthermore, the REMS website should be accessible directly through a search engine.

By way of example, we recommend you review the FDA-approved LEMTRADA REMS Website, which is available in the public domain via the following link: <https://www.lemtradarems.com/>

TEGSEDI REMS Patient Wallet Card

Your resubmission should include both a Word and PDF version.

TEGSEDI REMS Patient Status Form

The content of this material is still under discussion and Agency comments are forthcoming.

REMS Supporting Document

This document should be revised to align with the changes applied to the REMS document and appended materials. In general, the REMS supporting document should expand on information in the REMS document and provide additional information about the REMS, such as rationale supporting the need for each of the REMS requirements. More detail is needed to explain how pharmacies will verify safe-use conditions. It may be unrealistic to expect to audit (b) (4) of pharmacies that dispense Tegsedi. We recommend, instead, changing that requirement to "25% of certified pharmacies that have dispensed Tegsedi or one, whichever is greater," to minimize the burden of complying with the REMS. Additionally, your REMS supporting document should include a section explaining the distribution process.

Content of your Complete Resubmission:

Submit all content edits in Word documents with tracked changes, which makes review of these materials more efficient. We remind you that REMS communications materials must show the proposed formatting and design, including color scheme and logos.

To facilitate further review, revise your REMS proposal to reflect the changes indicated above and resubmit your complete REMS amendment within 14 calendar days, by May 4, 2018. Your complete REMS proposal should be submitted as separate documents in the same submission, to include a Word clean version, redlined Word version in tracked changes, and PDF version of each of the documents and appended materials. If certain materials, such as website screenshots, are not available as Word documents, PDF submissions will suffice.

Your resubmission should include the following:

- REMS document
- Prescriber Training
- Prescriber Knowledge Assessment
- Prescriber Enrollment Form
- Patient Guide
- Wallet Card
- (b) (4)
- Patient Status Form
- REMS Program Overview
- Pharmacy Enrollment Form
- REMS Website screen captures
- REMS supporting document, which includes the REMS Assessment Plan
- A single PDF file that includes a clean version of the REMS document compiled with a clean version of each appended REMS material, including REMS Website screen captures. This should not include the REMS supporting document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIN M SOUTH
04/20/2018

JAMIE C WILKINS PARKER
04/20/2018