

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### **APPLICATION NUMBER:**

**211172Orig1s000**

***Trade Name:*** Tegsedi injection, 189 mg/mL

***Generic or Proper Name:*** inotersen

***Sponsor:*** Ionis Pharmaceuticals, Inc.

***Approval Date:*** October 5, 2018

***Indication:*** Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

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**211172Orig1s000**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**211172Orig1s000**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring MD 20993

NDA 211172

**NDA APPROVAL**

Ionis Pharmaceuticals, Inc.  
Attention: Matt Buck, J.D.  
Vice President, Regulatory Affairs  
2855 Gazelle Court  
Carlsbad, CA 92010

Dear Mr. Buck:

Please refer to your New Drug Application (NDA) dated and received November 6, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tegsedi (inotersen) injection, 189 mg/mL.

We acknowledge receipt of your major amendment dated April 23, 2018, which extended the goal date by three months.

This new drug application provides for the use of Tegsedi (inotersen) injection for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Medication Guide, and Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on September 27, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 211172.**” Approval of this submission by FDA is not required before the labeling is used.

## **EXPIRY DATING PERIOD**

An expiration dating period of 18 months is assigned when the drug product packages are stored refrigerated at 2-8°C and protected from light. In addition, following distribution to the patients, the in-use shelf-life of 6 weeks is acceptable when the drug product is stored at up to 30°C (86°F) and protected from light.

## **ADVISORY COMMITTEE**

Your application for Tegsedi was not referred to an FDA advisory committee because the clinical trial design is acceptable, the efficacy findings were clear, and the safety profile, despite the considerable serious toxicity, was acceptable for the lethal disease being treated. Labeling will make prescribers fully aware of the risks, allowing them to inform patients and decide whether to use the drug.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of

adverse events, including those related to hypersensitivity or cytokine release syndrome that occur within one day of inotersen administration, to assess known serious risks of serious thrombocytopenia and glomerulonephritis, to assess signals of serious risks of stroke and cervicocephalic arterial dissection and of CNS vasculitis, or to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Tegsedi (inotersen) during pregnancy or an unexpected serious risk of carcinogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 3491-1 A clinical study to characterize adverse events occurring within one day of inotersen administration to adult patients with the polyneuropathy of hereditary transthyretin-mediated amyloidosis. Characterize the events in individual patients and overall with respect to time course of adverse event onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes. An adequate number of patients should be enrolled and followed throughout their treatment with inotersen to allow for the characterization of adverse events occurring within one day of inotersen administration (e.g., hypersensitivity, cytokine release syndrome).

The timetable you submitted on October 4, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	12/2019
Study Completion:	12/2024
Final Report Submission:	05/2025

- 3491-2 A prospective observational registry study in adult patients with the polyneuropathy of hereditary transthyretin-mediated amyloidosis recruited from the REMS registry. The primary objectives are to characterize the risks of serious thrombocytopenia, glomerulonephritis, stroke and cervicocephalic arterial dissection, and CNS vasculitis with respect to time course of onset, preventive laboratory monitoring, and identification of risk factors. An adequate number of patients should be enrolled and followed throughout their participation in the REMS registry to allow for the characterization of serious thrombocytopenia, glomerulonephritis, stroke and cervicocephalic arterial dissection, and CNS vasculitis. The protocol should specify an appropriate comparator population(s) to which observed incidence rates will be compared.

The timetable you submitted on October 4, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2019  
Final Protocol Submission: 12/2019  
Study Completion: 12/2024  
Final Report Submission: 05/2025

- 3491-3 Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Tegsedi (inotersen) during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

The timetable you submitted on October 4, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2018  
Final Protocol Submission: 10/2019  
Study Completion: 11/2030  
Final Report Submission: 11/2031

- 3491-4 A two-year carcinogenicity study of inotersen in rat.

The timetable you submitted on October 4, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2018

Submit clinical protocol(s) to your IND 113968 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o)**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under

21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tegsedi to ensure the benefits of the drug outweigh the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis.

Your REMS must also include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have determined that Tegsedi can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers who prescribe the drug have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

- Each patient using the drug is enrolled in a registry

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and that require that the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on November 6, 2017, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Tegsedti into interstate commerce.

The Tegsedti REMS Assessment Plan includes, but is not limited to, the following:

1. REMS Program Implementation (6-month and 12-month assessments only)
  - a. Date when Tegsedti is commercially available
  - b. Date when the REMS Website became active and is fully operational
  - c. Date when prescribers could become certified online or by fax
  - d. Date when the REMS Coordinating Center is established and fully operational
  - e. Date when the Compliance Assessment Committee (CAC) is established and fully operational
2. REMS Program Operation and Performance Data (per reporting period and cumulatively)
  - a. Number of visits and unique visits to the REMS website
  - b. Number of REMS materials downloaded for each material
  - c. REMS Program Coordinating Center Report
    - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler/distributors, other)
    - ii. Summary of frequently asked questions (FAQ) by stakeholder type
    - iii. Summary report of program problems reported and corrective actions resulting from issues identified
3. REMS Enrollment Statistics (per reporting period and cumulatively)
  - a. Healthcare Providers
    - i. Number of newly enrolled and active healthcare providers (have prescribed Tegsedti at least once during the reporting period) stratified by method of enrollment (online or fax), medical degree, medical specialty, practice type, and geographic location
  - b. Pharmacies/Distributors
    - i. Number of newly enrolled and active pharmacies (have dispensed Tegsedti) stratified by type of pharmacy, and geographic location

- ii. Number of entities distributing Tegsedi
  - iii. Number of shipments and vials of Tegsedi sent from the specialty pharmacies and specialty distributors
- c. Patients
- i. Number of newly enrolled and active patients in the REMS program (have received at least one prescription of Tegsedi during the reporting period) stratified by method of enrollment (online or fax), age, geographic location, and gender
  - ii. Number of discontinued patients. Include demographics of the discontinued patients and reasons for discontinuation.
4. Report on Patient Status Forms
- a. Number of Patient Status Forms expected, received, outstanding, and not due as of the cut-off date by the number of active patients
  - b. Number of Patient Status Forms not received within 90 calendar days during treatment. Include forms not received within 95 days and outreach activities performed to collect the forms.
  - c. Number of Patient Status Forms not received within 8 weeks following discontinuation of Tegsedi. Include outreach activities performed to collect the forms.
  - d. Number of Patient Status Forms not received within 115 calendar days. Include the number of patients who are not authorized to receive Tegsedi and the disposition of the patient.
  - e. Number of Patient Status Forms that reported a discontinuation, stratified by reasons. Include the demographics of discontinued patients.
  - f. Number and percent of healthcare provider responses attesting to patient compliance with required monitoring based on the Patient Status Form
  - g. Number and percent of patients whose healthcare provider attested as being compliant with the required monitoring based on the Patient Status Form
5. Post-Training Prescriber Knowledge Assessment (KA) (per reporting period and cumulatively)
- a. Number of completed post-training knowledge assessments for healthcare providers by the method of completion. Include the number of healthcare providers.
  - b. Number of attempts needed to complete and the number of healthcare providers
  - c. A summary of the most frequently missed questions
  - d. A summary of potential comprehension or perception issues identified with the Knowledge Assessments
  - e. Number of healthcare providers who did not pass the knowledge assessments
6. Tegsedi Utilization Data (per reporting period and cumulatively)
- a. Number and percentage of Tegsedi prescriptions (new and refills) dispensed stratified by:
    - i. pharmacy type
    - ii. method of dispensing authorization (on-line versus phone)
    - iii. healthcare provider specialty and practice type

iv. patient demographics (ex. age, gender)

7. REMS Compliance (per reporting period and cumulatively)

- a. Audits: Summary of audit activities conducted during the reporting period including but not limited to:
  - i. An overview of the audit plan for each stakeholder (certified pharmacies and distributors). Include the criteria for noncompliance for each stakeholder.
  - ii. The number of audits performed
  - iii. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements
  - iv. A summary report of deviations found, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans. Include a unique ID for each stakeholder that had deviations in order to track deviations by stakeholder over time.
  - v. A summary of pharmacy audits conducted. Include reasons and corrective and preventative actions taken for noncompliance.
  - vi. A summary of distributor audits conducted. Include reasons and corrective and preventative actions taken for noncompliance.
  - vii. Verification that the pharmacy's designated authorized representative remains the same annually. If different, include the number of new authorized representative and verification of pharmacy recertification.
- b. Healthcare Providers
  - i. The number of healthcare providers who were non-compliant with the Tegsedti REMS program requirements. Include a detailed root-cause analysis including sources of the reports and corrective and preventive actions taken.
  - ii. Number of prescriptions written by non-certified prescribers. Include a detailed root-cause analysis, whether the prescription was dispensed, and corrective and preventive actions taken.
  - iii. Number of healthcare providers that were de-certified and reasons for decertification. Include if any healthcare providers were re-certified.
- c. Pharmacies and Wholesalers/Distributors
  - i. The number of pharmacies and wholesalers/distributors that were non-compliant with the Tegsedti REMS program requirements. Include a detailed root-cause analysis including sources of the reports and corrective and preventive actions taken.
  - ii. Number of prescriptions dispensed by non-certified pharmacies. Include a detailed root-cause analysis and corrective and preventive actions taken.
  - iii. Number of shipments to non-certified pharmacies. Include a detailed root-cause analysis including sources of the reports and corrective and preventive actions taken.
  - iv. Number of prescriptions/shipments to patients without appropriate verification, such as ensuring that prescribers are certified or that patients are enrolled. Include a detailed root-cause analysis and corrective and preventive actions taken.

- v. Number of prescriptions/shipments to non-enrolled patients. Include a detailed root-cause analysis including sources of the reports and corrective and preventive actions taken.
  - vi. Number of prescriptions that were dispensed for more than a 30-day supply
  - vii. Number of pharmacies and wholesalers/distributors that were decertified and the reason for decertification. Include if any pharmacies and/or wholesaler/distributors were recertified.
- d. Patients
- i. Number of patients not enrolled in the REMS program or registry who were dispensed Tegsedi.
8. Safety Surveillance (per reporting period and cumulatively)
- a. Adverse event assessments of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis
    - i. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
    - ii. Include a line listing of all cases that includes: manufacturer control number, narrative, and assessment of causality
    - iii. Include adverse events reported in the REMS registry
    - iv. Include adverse events reported by pharmacies
  - b. Number of Patient Status Forms that reported discontinuation due to an event of serious bleeding with severe thrombocytopenia. Include if patients were diagnosed with glomerulonephritis.
  - c. Number of enrolled patients that experienced a treatment interruption, duration of the treatment interruption, and a summary of the root cause analysis and any adverse events resulting from the treatment interruption.
  - d. An evaluation (e.g., chart review) of prescribers' adherence to the monitoring requirements (platelet count, estimated GFR, urinalysis, and UPCR) and treatment modifications as described in the PI
9. Knowledge, Attitude and Behavior (KAB) Evaluation (beginning with the 12-month assessment and annually thereafter with each assessment report)
- a. Healthcare provider understanding of:
    - i. The risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with Tegsedi
    - ii. The need to counsel patients on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
    - iii. The need to enroll patients in the Tegsedi REMS program
    - iv. The need to submit documentation of periodic monitoring of patients to identify severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis
  - b. Patient understanding of:
    - i. How to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
    - ii. The need to have platelet count and renal function monitored

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication.
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS.
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211172 REMS CORRESPONDENCE**  
(insert concise description of content in bold capital letters, e.g.,  
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 211172 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 211172/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 211172/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 211172/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 211172/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

### **REMS REVISION FOR NDA 211172**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are available only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

### **REQUESTED PHARMACOVIGILANCE**

We request that you perform postmarketing surveillance for thrombocytopenia, serious bleeding with thrombocytopenia, glomerulonephritis and serious renal toxicity events, serious neurologic events, serious hepatobiliary events, serious events occurring within one day of Tegsedi administration, hypersensitivity adverse events, and ocular toxicity consistent with vitamin A deficiency. Provide comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Provide expedited reporting of the following events: serious events of bleeding with thrombocytopenia, glomerulonephritis, and serious hepatobiliary events.

In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Tegsedi therapy, the time from first Tegsedi dose to adverse event onset, the time from last Tegsedi dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome.

Include analyses of the events by age. Include a comparison to background rates in the general population (overall and stratified by age), as well as background rates (if available) for patients with hereditary transthyretin amyloidosis (overall and stratified by age).

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or [fannie.choy@fda.hhs.gov](mailto:fannie.choy@fda.hhs.gov).

Sincerely,

*(See appended electronic signature page)*

Robert Temple, M.D.  
Deputy Director (Acting)  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling  
REMS

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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