NDA 211172/S-012

SUPPLEMENT APPROVAL

Akcea Therapeutics, Inc.
Attention: Nancy Johansen
Executive Director, Global Regulatory Affairs
2850 Gazelle Court
Carlsbad, CA 92010

Dear Ms. Johansen:

Please refer to your supplemental new drug application (sNDA) dated September 9, 2022, received September 9, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tegsedi (inotersen) injection.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Tegsedi risk evaluation and mitigation strategy (REMS).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tegsedi was originally approved on October 5, 2018, and the most recent REMS modification was approved on March 31, 2022. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

- addition of the *Healthcare Provider Reminder Letter for Patient Status Form Submission* as a new REMS material and changes to the REMS Document to reflect the requirement to disseminate this letter
- update to the existing Prescriber Training to add the Patient Status Form Timing Requirements Reminder Sheet chart as an appendix

Your proposed modified REMS, submitted on September 9, 2022, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 5, 2018.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication (per the two previous, current, and cumulative reporting periods)

1. Number of visits and unique visits to the REMS website
2. Number of REMS materials downloaded for each material
3. A summary of the extent to which the REMS materials reached the intended stakeholders.
4. Number of Health Care Provider Reminder Letters for Patient Status Form Submission sent via email that were successfully delivered, opened, and unopened stratified by time sent:
    a. Upon certification
    b. Annually

Program Implementation and Operations (per the two previous, current, and cumulative reporting periods)

1. REMS Enrollment Statistics

a. Healthcare Providers

i. Number of newly enrolled and active healthcare providers (have prescribed Tegsedi at least once during the reporting period) stratified by method of enrollment (online or fax), medical degree, medical specialty, practice type, and geographic location.

Pharmacies/Distributors

i. Number of newly enrolled and active pharmacies (have dispensed Tegsedi) 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.

b. 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.

2. 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. Include the number of unique patients associated with these forms.

   e. Number of ***Patient Status Forms*** that reported a discontinuation, stratified by reasons (compile specified reasons for discontinuations reported as "Other"). Include the demographics of discontinued patients.

   f. Number and percentage of ***Patient Status Forms*** on which the healthcare provider attested to being compliant with the required monitoring. Include the number and percentage of unique healthcare providers and patients associated with the forms.

3. REMS Compliance

   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 newly authorized representatives and verification of pharmacy recertification.

b. Healthcare Providers

i. The number of healthcare providers who were non-compliant with the Tegsedi 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 Tegsedi 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 that were decertified and wholesalers-distributors that were deauthorized and the reason for decertification or deauthorization. Include if any pharmacies or wholesaler/distributors were recertified or reauthorized.

d. Patients

i. Number of patients not enrolled in the REMS program or registry who were dispensed Tegsedi.

5. REMS Call Center

a. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler/distributors, other)

b. Summary of frequently asked questions (FAQ) by stakeholder type

c. Summary report of program problems reported and corrective actions resulting from issues identified

6. Tegsedi Utilization Data

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 (e.g., age, geographic location, gender)

Knowledge (per reporting period and cumulatively)

1. Healthcare provider understanding of:
    a. The risk of serious bleeding with severe thrombocytopenia and the risk of glomerulonephritis associated with Tegsedi
    b. The need to counsel patients on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
    c. The need to enroll patients in the Tegsedi REMS program
    d. The need to submit documentation of periodic monitoring of patients to identify severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis.
2. Patient understanding of:
    a. How to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis
    b. The need to have platelet count and renal function monitored
3. Post-Training Knowledge Assessment (KA)
    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 the KA 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

Health Outcomes and or/ Surrogates of Health Outcomes (per the two previous, current, and cumulative reporting periods)

1. Safety Surveillance
   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 Prescribing Information (PI).

Overall Assessment of REMS Effectiveness

1. 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 1 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) of the FDCA. 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 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 that 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 REMS modifications*, 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 ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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

or

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 LABELING CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

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 REVISIONS 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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF 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 Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

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

If you have any questions, contact Terry Harrison, Safety Regulatory Project Manager, at terry.harrison@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sally Yasuda, MS, PharmD
Deputy Director for Safety
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):
- REMS

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/

SALLY U YASUDA
03/08/2023 03:47:01 PM