NDA 217686/S-002

SUPPLEMENT APPROVAL

Idorsia Pharmaceuticals Ltd.
c/o: Idorsia Clinical Development US Inc.
Attention: Bradford Kirk Perry, PharmD, RPh
Director, US Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 150
Cherry Hill, NJ 08002

Dear Bradford Perry:

Please refer to your supplemental new drug application (sNDA) dated and received June 12, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tryvio (aprocitentan) Tablets.

This Changes Being Effected supplemental new drug application provides for proposed modifications to the approved Tryvio risk evaluation and mitigation strategy (REMS).

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tryvio was originally approved on March 19, 2024. 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:

- Changes to the REMS website to enhance operation flow and accommodate technical capabilities of the new REMS vendor
- Changes to methods available to stakeholders for contacting the REMS Coordinating Center
- Editorial revisions of layout and incorporation of Tryvio logo throughout REMS materials

Your proposed modified REMS, submitted on June 12, 2024, amended, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 19, 2024.

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

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

REMS Implementation and Operations:

1. REMS Website
   a. Date REMS Website went live (first assessment report only)
   b. Number of total visits and number of unique visits to the REMS Website
   c. Number and type of REMS materials downloaded or printed for each material
   d. Summary of outages or problems with the operation of the REMS Website

2. REMS Implementation (first assessment report only)
   a. Date of first commercial availability of Tryvio
   b. Date of Tryvio REMS launch
   c. Date that each stakeholder (e.g., healthcare providers, pharmacies, wholesaler/distributors) could become certified/authorized
   d. Date when the REMS Coordinating Center was established and fully operational

3. REMS Infrastructure and Performance
   a. REMS Coordinating Center
      i. Number of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacies, wholesaler/distributors, other)
      ii. Summary of reasons for calls (e.g., authorization to dispense, enrollment question, location of a pharmacy) and by stakeholder type (e.g., healthcare providers, pharmacies, wholesaler/distributors, patients, authorized representative, other). Limit the summary to the top five reasons for calls by each stakeholder group.
      iii. If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues, and how these issues were resolved
      iv. Summary of frequently asked questions (FAQs) by stakeholder type

4. REMS Certification and Enrollment
   a. Certified Pharmacies
      i. Number and percentage of newly certified pharmacies, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
      ii. Method of pharmacy certification (i.e., online, fax)
      iii. Total number of certified pharmacies at the end of the reporting period, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
      iv. Number and percentage of active certified pharmacies (i.e., have dispensed Tryvio), stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)

b. Certified Healthcare Providers
   i. Number and percentage of newly certified healthcare providers, stratified by medical specialty (e.g., cardiology, internal medicine, etc.)
   ii. Method of healthcare provider certification (i.e., online, fax)
   iii. Total number of certified healthcare providers at the end of the reporting period
   iv. Number and percentage of active certified healthcare providers (i.e., have prescribed Tryvio)

c. Authorized Wholesaler/Distributors
   i. Number of newly contracted wholesaler/distributors
   ii. Number of active (i.e., have shipped Tryvio) wholesaler/distributors

5. REMS Utilization

   a. Number of tablets sent to certified prescribers, certified pharmacies, stratified by type of pharmacy

6. REMS Compliance

   a. Audits: Provide a report of audit findings for each stakeholder (i.e., certified inpatient pharmacies; certified outpatient pharmacies; authorized wholesalers/distributors) including but not limited to:
      i. A copy of the audit plan for each stakeholder
      ii. The number of audits expected, and the number of audits conducted
      iii. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for group of audited stakeholders
      iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
      v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      vi. Confirm documentation of completion of training for relevant staff
      vii. Verify the existence of documented processes and procedures for complying with the REMS
      viii. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

   b. Non-Compliance: Provide a summary of the non-compliance identified, including but not limited to:
      i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
      ii. The number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
         1. The unique identifier (ID(s)) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over

time
2. The source of the non-compliance data
3. The results of the root cause analysis
4. What action(s) were taken in response and whether any follow up is planned

iii. Number and percentage of certified healthcare providers that were non-compliant with the REMS requirements
1. Number of certified healthcare providers that had certification suspended or revoked. Include the reasons for the action.

iv. Number and percentage of authorized wholesaler/distributors that were non-compliant with the REMS requirements
1. Number of shipments sent to non-certified pharmacies. Include the source of the report, corrective actions taken to prevent future occurrences, and the outcome of such actions

v. Number and percentage of certified pharmacies that were non-compliant with the REMS requirements, stratified by setting (e.g., inpatient, outpatient)
1. Number of certified pharmacies that had certification suspended or revoked. Include the reasons for the action

vi. Outpatient pharmacy-related REMs Dispense Authorizations (RDAs) compliance
1. The number of RDAs issued
2. The number of RDA requests that were not authorized because the prescriber is not certified
3. Summary of RDA compliance issues (e.g., pharmacy did not request RDA, pharmacy dispensed without RDA, etc.) identified in audits, corrective actions, and resolution.

vii. For certified inpatient and outpatient pharmacies that are audited: the number and percentage of patients who received the patient material, Risk of Birth Defects with Tryvio, stratified by pharmacy type (inpatient, outpatient specialty, outpatient retail)

viii. For all other non-compliance with the REMS requirements, provide source of
Non-compliance report, and the corrective action taken

Knowledge

7. Post-training Knowledge Assessment
a. Number of healthcare providers who completed post-training knowledge assessment. Include method of completion and number of attempts needed to complete.
b. Number of healthcare providers who did not pass the knowledge assessment.
c. A summary of the most frequently missed questions.
d. A summary of potential comprehension or perception issues identified with the knowledge assessment (first assessment report only)

8. Evaluation of Knowledge of the Tryvio REMS and Risks of Tryvio
   a. An evaluation of certified healthcare providers' knowledge, attitudes, and behaviors (to be conducted annually from the date of REMS approval) related to:
      i. The risks of embryo-fetal toxicity associated with Tryvio
      ii. The need to counsel patients who can become pregnant about:
         1. The risks of embryo-fetal toxicity associated with Tryvio
         2. The recommendation for pregnancy testing prior to initiating treatment, monthly during treatment, and for one month after discontinuing treatment
         3. The need for patients who can become pregnant to use acceptable contraception
   b. Qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with Tryvio" (to be conducted once initially).

Health Outcomes and/or Surrogates of Health Outcomes

9. An estimation of the percent pregnancy rate per reporting period and cumulatively, reported as:
   a. Percentage pregnancy rate, calculated as the number of pregnancies reported divided by the number of women of reproductive potential who were exposed to Tryvio
   b. Pregnancy incidence rate (in person-years), calculated as the number of pregnancies reported divided by the amount of person-time that women of reproductive potential were exposed to Tryvio

Overall Assessment of REMS Effectiveness

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) 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 217686 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 217686 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 217686/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217686/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217686/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 217686/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 217686

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.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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 Lori Anne Wachter, RN, BSN, RAC – Drugs (US), Regulatory Project Manager for Safety, at 301 796-3975 or lori.wachter@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
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/

MARY R SOUTHWORTH
08/07/2024 01:38:18 PM