NDA 217686/S-004

SUPPLEMENT APPROVAL

Idorsia Pharmaceuticals, Inc.
Attention: Bradford Kirk Perry, PhD., Rph
Head of US Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:

Please refer to your supplemental new drug application (sNDA) dated and received March 18, 2025, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tryvio (aprocitentan) tablets.

This Prior Approval sNDA provides for changes to the approved Tryvio label to remove text regarding the Tryvio REMS and proposed modifications to the approved Tryvio risk evaluation and mitigation strategy (REMS). This supplement is in response to our March 11, 2025, REMS Modification Notification letter.

APPROVAL & LABELING

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tryvio was originally approved on March 19, 2024, and the most recent REMS modification was approved on December 9, 2024. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Because a REMS is no longer necessary to ensure the benefits of the drug outweigh the risk of embryo-fetal toxicity and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated March 11, 2025.

Elements to Assure Safe Use: We have determined that elements to assure safe use are no longer necessary based on an evaluation of human fetal outcomes reported from 2001 to 2024 after exposure to a drug in the endothelin receptor antagonist (ERA) pharmacologic class. These data have not shown a pattern of congenital malformations

consistent with what was observed in animal embryo-fetal toxicity studies that supported the need for a REMS. Given the re-evaluation of the extent of the clinical risk based on animal findings, we have determined that the labeling is sufficient for conveying information about the embryo-fetal risk and its mitigation.

Implementation System: In addition, because the element to assure safe use requiring that pharmacies, practitioners, or health care settings that dispense the drug be specially certified is no longer necessary, the implementation system is also no longer necessary as an element of the REMS.

Therefore, because the elements to assure safe use and the implementation system are no longer necessary to ensure the benefits of the drug outweigh the risk, and to minimize the burden on the healthcare system of complying with a REMS, a REMS is no longer required for Tryvio.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

---

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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).

---

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENHANCED PHARMACOVIGILANCE

We request that you provide a summary analysis of reports of pregnancy and embryo-fetal and neonatal toxicity as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], for 3 years following approval of the REMS Modification.

Your analysis should include interval and cumulative data from clinical trials, postmarketing reports, and published literature relative to the date of the approval of the REMS modification. Your analysis should include at a minimum the cumulative number of reported pregnancies, pregnancy outcome [such as live birth, stillbirth, miscarriage, elective termination, congenital anomaly and type], and an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, and underlying risk factors.

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
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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
04/02/2025 05:07:34 PM