NDA 216403/S-006

SUPPLEMENT APPROVAL

Travere Therapeutics, Inc.
Attention: Lynley Thinnes
Vice President, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Lynley Thinnes:

Please refer to your supplemental new drug application (sNDA) dated and received March 13, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Filspari (sparsentan) tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated March 13, 2025.

We also acknowledge receipt of your major amendments dated December 19 and 24, 2025, and January 6 and 9, 2026, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for the addition of a new indication for Filspari (sparsentan) to reduce proteinuria in adult and pediatric patients aged 8 years and older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome, and proposed modifications to the approved Filspari REMS.

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.

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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.

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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Filspari was originally approved on February 17, 2023, and the most recent REMS modification was approved on August 27, 2025. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of:

- Inclusion of the FSGS indication in the Prescriber and Pharmacy Guide, Patient Guide, and REMS website, to align with labeling updates

[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.

Your proposed modified REMS, submitted on March 13, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on February 17, 2023.

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 (where applicable) unless otherwise noted.

REMS Implementation and Operations

1. **REMS Certification and Enrollment Statistics**

    a. Healthcare Providers

        i. Number and percentage of newly certified healthcare providers, and the number and percentage of active healthcare providers (i.e., who have prescribed Filspari) stratified by medical specialty and geographic region (as defined by United States (US) Census)

    b. Pharmacies

        i. Number and percentage of newly certified pharmacies, and the number and percentage of active certified pharmacies (i.e., have dispensed Filspari) stratified by pharmacy type (i.e., inpatient and outpatient) and geographic region (as defined by US Census)

    c. Patients

        i. Number and percentage of newly enrolled patients and the number and percentage of active patients (i.e., have received Filspari) stratified by geographic region (defined by US Census) and stratified by age (<8 years, 8 to <18 years, 18 to <45 years, 45 to <65 years, 65 years and older)

    d. Wholesaler/Distributors

        i. Number and percentage of newly enrolled wholesaler/distributors and the number and percentage of active wholesaler / distributors (i.e., have shipped Filspari)

2. **REMS Utilization Data**

a. Number and percentage of unique patients who received Filspari, stratified by new and total number of patients

b. Number and percentage of unique patients who received Filspari, stratified by age (<8 years, 8 to <18 years, 18 to <45 years, 45 to <65 years, 65 years and older)

c. Number and percentage of prescriptions (first-fills and refills) dispensed for patients stratified by:

    i. Healthcare Provider Specialty

3. **REMS Infrastructure and Performance**

    a. REMS Coordinating Center

        i. Number of contacts by stakeholder type (i.e., patients, healthcare providers, pharmacies, wholesaler(s)/distributor(s), other)

        ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by reporter (authorized representative, pharmacy, healthcare provider, patient, other)

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

        iv. Summary report of REMS-related problems identified and resulting corrective actions

        v. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues

    b. **REMS Website**

        i. Number of visits and unique visits to the **REMS Website**

        ii. Number of REMS materials downloaded and printed for each material

4. **Pharmacy and Distributor Audit Summary**

    a. Provide a report of audit findings for each stakeholder (i.e., certified inpatient pharmacies; certified outpatient pharmacies; the REMS Coordinating Center; 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. Use a unique ID for stakeholders that had deviations to track deviations by stakeholders over time

vii. Confirm documentation of completion of training for relevant staff

viii. Verify the existence of documented processes and procedures for complying with the REMS

ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

5. **Filspari REMS Compliance**

a. 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

b. Number of Filspari prescriptions dispensed that were written by non-certified or deactivated prescribers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions

c. Number of prescriptions dispensed by non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions

d. Number of prescriptions dispensed:

   i. with an expired REMS dispensing verification code

   ii. without a REMS dispensing verification code

e. Number of shipments sent to non-certified pharmacies, source of report(s), actions taken to remove Filspari from these pharmacies, actions taken to prevent future occurrences and outcome of such actions

f. Number and percentage of pharmacies who were non-compliant with the Filspari REMS requirements (i.e., did not confirm liver tests and counseling)

g. Number and percentage of pharmacies by type (i.e., inpatient, outpatient) that did not provide verification of the authorized representative every 2 years

h. The number of certified prescribers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action

i. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in dispensing/shipment of ten or more days) focusing only on delays caused by missed liver testing. Include a root cause analysis to identify why testing was not completed along with the protocol used to conduct the root cause analysis. For each treatment interruption, include:

   i. The mean and median duration (including the standard deviation) of the observed treatment interruptions; and

   ii. Any adverse events resulting from the treatment interruption

j. Number of prescriptions dispensed of greater than 90-days' supply (outpatient) or greater than 30-days' supply (inpatient), and a breakdown

of reasons for the dispenses (i.e., Prescriber Authorization Based on Medical Judgement, Pharmacy Non-Compliance, Patient Travel, or Insurance Requirements). Include any corrective actions as appropriate

k. Unintended system interruptions and corrective actions taken

l. Other barriers or delays in product dispensing and corrective actions taken

m. For all noncompliance with the Filspari REMS requirements, provide source of noncompliance report(s), and any corrective action(s) or resolution(s)

Safe Use Behaviors

6. **Liver Testing**

a. Number and percentage of all dispenses associated with confirmation from a certified pharmacy that liver testing was performed when required, or the prescriber authorized the refill prior to each dispense

b. If established threshold for metric 6.a. above is not met, provide a root cause analysis of why the threshold was not met, and a proposed plan for specific measures or modifications to the REMS to meet the established threshold

c. Number of one-time authorizations by prescribers (i.e., prescriber used clinical judgement and allowed the dispense without liver testing)

i. Number and percentage authorized for missing liver testing verification

Health Outcomes and/or Surrogates of Health Outcomes

7. **Hepatotoxicity**

    a. Provide new or updated safety findings, if any, to inform the incidence, severity, and frequency of hepatoxicity, and an assessment of the effectiveness of the REMS strategy in mitigating the risk

Overall Assessment of REMS Effectiveness

8. 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 216403 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 216403 REMS ASSESSMENT**

or

NEW SUPPLEMENT FOR NDA 216403 /S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 216403/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 216403/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 216403/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 216403

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word and PDF format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word and PDF format are 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.

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]

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

If you have any questions, please contact Melissa Button, Regulatory Health Project Manager, at 240-402-1995 or email at melissa.button@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

ALIZA M THOMPSON
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