CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

216403Orig1s005

Trade Name:	FILSPARI
Generic or Proper Name:	(sparsentan)
Sponsor:	Travere Therapeutics INC
Approval Date:	August 27, 2025
Indication:	FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

CENTER FOR DRUG EVALUATION AND RESEARCH

216403Orig1s005

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APPLICATION NUMBER:

216403Orig1s005

APPROVAL LETTER

NDA 216403/S-005

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 on October 28, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Filspari (sparsentan) tablets.

This Prior Approval sNDA provides for a change to the frequency of the liver monitoring and corresponding changes to the approved labeling and proposed modifications to the approved Filspari risk evaluation and mitigation strategy (REMS). This supplement is, in part, 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.

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]

[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.

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 September 5, 2024. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

- Change in liver monitoring and patient counseling frequency to every 3 months during treatment with Filspari
- Change in outpatient pharmacy dispensing to 90-days' supply to align with the changes in liver testing and counseling cadence
- Updates to the REMS materials to align with the change in liver testing frequency and patient counseling cadence

In addition, in order to ensure the benefits of Filspari outweigh its risks 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 Notification letter dated March 11, 2025.

Elements to Assure Safe Use: We have determined that elements to assure safe use for the risk of embryofetal toxicity 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 labeling is sufficient for conveying information about the embryo-fetal risk and its mitigation. ETASU required to mitigate the risk of hepatotoxicity are not impacted by this change.

Implementation System: In addition, because the elements to assure safe use related to the risk of embryo-fetal toxicity requiring that pharmacies, practitioners, or health care settings that dispense the drug be specially certified, and that the drug be dispensed to patients with documentation of safe use conditions are no longer necessary, the implementation system for the elements to assure safe use related to the risk of embryfetal toxicity is also no longer necessary as an element of the REMS. Aspects of the implementation system for the ETASU required to mitigate the risk of hepatotoxicity are not impacted by this change.

Your proposed modified REMS, submitted on August 5, 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 items:

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)

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 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 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.

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. Information and Instructions for completing the form can be found at FDA.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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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).

ENHANCED PHARMACOVIGILANCE

We request that you provide a summary analysis of reports of pregnancy and embryofetal 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, please contact Anna Park, Regulatory Project Manager, at (301) 796-1129 or anna.park@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Selena DeConti, PharmD, MPH
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

ENCLOSURES:

- 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/

SELENA D DECONTI
08/27/2025 01:15:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FILSPARI® safely and effectively. See full prescribing information for FILSPARI®.

FILSPARI® (sparsentan) tablets, for oral use
Initial U.S. Approval: 2023

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **FILSPARI is only available through a restricted distribution program called the FILSPARI Risk Evaluation and Mitigation Strategies (REMS) because of the risk of hepatotoxicity (5.2):**
  - **Some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure (5.1).**
  - **Measure liver aminotransferases and total bilirubin prior to initiation of treatment and ALT and AST every 3 months during treatment (2.2, 2.6, 5.1).**
  - **Interrupt treatment and closely monitor patients developing aminotransferase elevations more than 3-times Upper Limit of Normal (ULN) (2.2, 2.6).**
- **Based on animal data, FILSPARI may cause fetal harm if used during pregnancy and is contraindicated in pregnancy (4, 5.3, 8.1).**
  - **For patients who can become pregnant, exclude pregnancy prior to the initiation of treatment with FILSPARI (2.3, 5.3, 8.3).**
  - **Use effective contraception prior to initiation of treatment, during treatment, and for two weeks after stopping FILSPARI (4, 5.3, 8.1, 8.3).**
  - **When pregnancy is detected, discontinue FILSPARI as soon as possible (5.3).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	8/2025
Indications and Usage	9/2024
Dosage and Administration, Monitoring (2.2)	8/2025
Dosage and Administration, Pregnancy Testing (2.3)	8/2025
Warnings and Precautions (5)	8/2025

---------- INDICATIONS AND USAGE----------

FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression (1, 12.1).

----------DOSAGE AND ADMINISTRATION----------

- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs) (2.1, 4, 7.1).
- Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to 400 mg once daily, as tolerated. When resuming FILSPARI after an interruption, consider re-titration (2.4).
- Instruct patients to swallow tablets whole with water prior to the morning or evening meal (2.5).

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 200 mg and 400 mg (3).

---------- CONTRAINDICATIONS ----------

- Pregnancy (4).
- Concomitant use with angiotensin receptor blockers (ARBs), ERAs, or aliskiren (4).

---------- WARNINGS AND PRECAUTIONS ----------

- Hypotension (5.4)
- Acute Kidney Injury (5.5)
- Hyperkalemia (5.6)
- Fluid Retention (5.7)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥5%) are hyperkalemia, hypotension (including orthostatic hypotension), peripheral edema, dizziness, anemia, and acute kidney injury (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Travere Therapeutics at 1-877-659-5518 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Strong CYP3A inhibitors: Avoid concomitant use. Increased sparsentan exposure (2.7, 7.2, 12.3).
- Moderate CYP3A inhibitors: Monitor adverse reactions. Increased sparsentan exposure (7.2, 12.3).
- Strong CYP3A inducers: Avoid concomitant use. Decreased sparsentan exposure (7.3, 12.3).
- Antacids: Avoid use within 2 hours before or after use of sparsentan. May decrease exposure to sparsentan (7.4, 11).
- Acid reducing agents: Avoid concomitant use. May decrease exposure to sparsentan (7.4).
- Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase (COX-2) inhibitors: Monitor for signs of worsening renal function. Increased risk of kidney injury (7.5).
- CYP2B6, 2C9, and 2C19 substrates: Monitor for substrate efficacy. Decreased exposure of these substrates (7.6, 12.3).
- Sensitive P-gp and BCRP substrates: Avoid concomitant use. Increased exposure to substrates (7.7, 12.3).
- Agents Increasing Serum Potassium: Increased risk of hyperkalemia, monitor serum potassium frequently (5.6, 7.8).

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

Because of the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients, and pharmacies must enroll in the program *[see Warnings and Precautions (5.1, 5.2)]*.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. Measure transaminases and bilirubin before initiating treatment and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3-times ULN *[see Dosage and Administration (2.2, 2.6), Warnings and Precautions (5.1)]*.

FILSPARI should generally be avoided in patients with elevated aminotransferases (>3-times ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity *[see Dosage and Administration (2.2, 2.6), Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

FILSPARI is contraindicated for use during pregnancy because it may cause fetal harm if used by pregnant patients. Therefore, in patients who can become pregnant, exclude pregnancy prior to initiation of FILSPARI. Advise use of effective contraception before the initiation of treatment, during treatment, and for two weeks after discontinuation of treatment with FILSPARI. When pregnancy is detected, discontinue FILSPARI as soon as possible *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

1. INDICATIONS AND USAGE

FILSPARI is indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

2. DOSAGE AND ADMINISTRATION

2.1. General Considerations

Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs) *[see Contraindications (4), Drug Interactions (7.1)]*.

2.2. Monitoring

Initiate treatment with FILSPARI only after measuring aminotransferase levels and total bilirubin. Avoid initiation in patients with elevated aminotransferases greater than 3 times ULN. Continue required monitoring every 3 months during treatment with FILSPARI *[see Dosage and Administration (2.6), Warnings and Precautions (5.1)]*.

2.3. Pregnancy Testing

Exclude pregnancy before initiating treatment with FILSPARI *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.4. Recommended Dosage

Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily *[see Drug Interactions (7.2)]*.

2.5. Administration

- Instruct patient to swallow tablets whole with water prior to the morning or evening meal.
- Maintain the same dosing pattern in relationship to meals.
- If a dose is missed, take the next dose at the regularly scheduled time. Do not take double or extra doses.

2.6. Dosage Adjustment for Aminotransferase Elevations

If aminotransferase levels increase, adjust monitoring and treatment plan according to Table 1.

Do not resume treatment in patients who have experienced clinical symptoms of hepatotoxicity or in patients whose hepatic enzyme levels and bilirubin have not returned to pretreatment levels.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations Greater Than 3 Times ULN

ALT/AST levels	Treatment and monitoring recommendations
Greater than 3 times and less than or equal to 8 times ULN	Confirm elevation with a repeat measure. If confirmed, interrupt treatment, and monitor aminotransferase levels and bilirubin at least weekly, and INR as needed, until the levels return to pretreatment values and the patient is asymptomatic. Do not resume treatment if any of the following occurs without other cause found: • ALT or AST greater than 3 times ULN and total bilirubin greater than 2 times ULN or INR greater than 1.5 • ALT or AST greater than 3 times ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (greater than 5% eosinophils) • ALT or AST greater than 5 times ULN for more than 2 weeks If treatment is resumed, initiate FILSPARI at 200 mg once daily, with reassessment of hepatic enzyme levels and bilirubin within 3 days. Close monitoring is required in these patients *[see Dosage and Administration (2.2,2.4)]*.
Greater than 8 times ULN	Stop treatment permanently if no other cause found.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; ULN = upper limit of normal.

2.7. Dosage Modification for Concomitant Use with Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors with FILSPARI.

If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI *[see Drug Interactions (7.2)]*.

3. DOSAGE FORMS AND STRENGTHS

FILSPARI is supplied as film-coated, modified oval, white to off-white tablets debossed on one side and plain on the other in the following strengths:

200 mg debossed with “105”
400 mg debossed with “021”

4. CONTRAINDICATIONS

Use of FILSPARI is contraindicated in patients who are pregnant *[see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

5. WARNINGS AND PRECAUTIONS

5.1. Hepatotoxicity

Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge *[see Adverse Reactions (6.1)]*. While no concurrent elevations in bilirubin greater than 2-times ULN or cases of liver failure were observed in FILSPARI-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and then every 3 months during treatment *[see Dosage and Administration (2.2)]*.

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended *[see Dosage and Administration (2.6)]*.

Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity *[see Dosage and Administration (2.2, 2.6)]*.

Avoid initiation of FILSPARI in patients with elevated aminotransferases (greater than 3-times ULN) because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity *[see Dosage and Administration (2.2, 2.6), and Warnings and Precautions (5.2)]*.

5.2. FILSPARI REMS

For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity *[see Warnings and Precautions (5.1)]*.

Important requirements of the FILSPARI REMS include the following:

- Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.

- All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements *[see Dosage and Administration (2.2, 2.6), Warnings and Precautions (5.1)].*
- Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

Further information is available at www.filsparirems.com or 1-833-513-1325.

5.3. Embryo-Fetal Toxicity

Based on data from animal reproduction studies, FILSPARI may cause fetal harm when administered to a pregnant patient and is contraindicated for use during pregnancy. The available human data for endothelin receptor antagonists do not establish the presence or absence of fetal harm related to the use of FILSPARI. Counsel patients who can become pregnant of the potential risk to a fetus. Exclude pregnancy before initiating treatment with FILSPARI. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for two weeks after discontinuation of treatment with FILSPARI. When pregnancy is detected, discontinue FILSPARI as soon as possible *[see Dosage and Administration (2.3), Contraindications (4), Use in Specific Populations (8.1, 8.3)].*

5.4. Hypotension

Hypotension has been observed in patients treated with ARBs and endothelin receptor antagonists (ERAs) and was observed in clinical studies with FILSPARI. In the PROTECT trial, there was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan *[see Adverse Reactions (6.1)].*

In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status.

If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized.

5.5. Acute Kidney Injury

Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.

5.6. Hyperkalemia

Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease or taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required *[see Dosage and Administration (2.4), Adverse Reactions (6.1)]*.

5.7. Fluid Retention

Fluid retention may occur with endothelin receptor antagonists and has been observed in clinical studies with FILSPARI *[see Adverse Reactions (6.1)]*. FILSPARI has not been evaluated in patients with heart failure.

If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.

6. ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the label include:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Hypotension *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Hyperkalemia *[see Warnings and Precautions (5.6)]*
- Fluid Retention *[see Warnings and Precautions (5.7)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of FILSPARI was evaluated in PROTECT (NCT03762850), a randomized, double-blind, active-controlled clinical study in adults with IgAN.

The data below reflect FILSPARI exposure in 202 patients with a median duration of 110 weeks.

The most common adverse reactions are presented in Table 2.

Table 2: Adverse Reactions Reported in 2% or More of Subjects Treated with FILSPARI

	FILSPARI (N = 202) n (%)	Irbesartan (N = 202) n (%)
Hyperkalemia[1]	34 (17)	27 (13)
Hypotension (including orthostatic hypotension)	33 (16)	13 (6)
Peripheral edema[1]	33 (16)	29 (14)
Dizziness[1]	32 (16)	14 (7)
Anemia	16 (8)	9 (4)
Acute kidney injury	12 (6)	5 (2)
Transaminase elevations[2]	7 (3.5)	8 (4.0)

[1] Includes related terms.
[2] Elevations in ALT or AST greater than 3-fold ULN.

Laboratory Tests

Initiation of FILSPARI may cause an initial small decrease in estimated glomerular filtration rate (eGFR) that occurs within the first 4 weeks of starting therapy and then stabilizes.

The incidence of a hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (19%) compared to the irbesartan arm (13%). This decrease is thought to be in part due to hemodilution. There were no treatment discontinuations due to anemia or hemoglobin decrease in the PROTECT study.

7. DRUG INTERACTIONS

7.1. Renin-Angiotensin System Inhibitors and ERAs

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren [see Dosage and Administration (*2.1*), Contraindications (*4*)].

Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).

7.2. Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration *[see Dosage and Administration (2.4, 2.7), Clinical Pharmacology (12.3)]*.

Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7)].* No FILSPARI dose adjustment is needed.

Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of FILSPARI adverse reactions.

7.3. Strong CYP3A Inducers

Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may reduce FILSPARI efficacy.

7.4. Antacids and Acid Reducing Agents

Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility *[see Description (11)]*. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy.

7.5. Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure *[see Warnings and Precautions (5.5)]*. These effects are usually reversible.

7.6. CYP2B6, 2C9, and 2C19 Substrates

Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates *[see Clinical Pharmacology (12.3)]*, which may reduce efficacy related to these substrates.

7.7. P-gp and BCRP Substrates

Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

7.8. Agents Increasing Serum Potassium

Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia *[see Warnings and Precautions (5.6)].*

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on data from animal reproductive toxicity studies, FILSPARI may cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy *[see Contraindications (4)].* Available data from reports of pregnancy in clinical trials with FILSPARI are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available data from postmarketing reports and published literature over decades of use with ERA in the same class as FILSPARI have not identified an increased risk of fetal harm; however, these data are limited. Methodological limitations of these postmarketing reports and published literature include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and missing data. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal ERA use. In animal reproduction studies, oral administration of sparsentan to pregnant rats throughout organogenesis at 10-times the maximum recommended human dose (MRHD) in mg/day caused teratogenic effects in rats, including craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights *(see Data).* Advise pregnant patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In embryo-fetal development studies in pregnant rats and rabbits, teratogenicity and/or developmental toxicity were observed, which were attributed to the antagonism of endothelin type A (ET_A) and angiotensin II type 1 (AT_1) receptors.

In pregnant rats, oral administration of sparsentan throughout organogenesis at doses of 80, 160, and 240 mg/kg/day resulted in dose-dependent teratogenic effects in the

form of craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights at all doses tested. The area under the curve (AUC) at the lowest dose tested (80 mg/kg/day) was approximately 10 times the AUC at the MRHD of 400 mg/day. In pregnant rabbits, oral administration of sparsentan throughout organogenesis at doses of 2.5, 10 and 40 mg/kg/day resulted in maternal death and abortions at 10 and 40 mg/kg/day which provided exposures approximately 0.1 times and 0.2 times the AUC at the MRHD, respectively. An increase in a fetal variation (supernumerary cervical ribs) occurred at the high dose of 40 mg/kg/day.

In the pre- and postnatal development study in rats, oral administration of sparsentan during pregnancy and the lactational period at doses of 5, 20, or 80 mg/kg/day resulted in maternal death, body weight loss/reduced body weight gain, and adverse clinical signs at 80 mg/kg/day. An increase in pup deaths occurred at 80 mg/kg/day (approximately 10 times the AUC at MRHD) during the neonatal period through weaning, and decreased growth occurred at ≥ 20 mg/kg/day (approximately 2.6 times the AUC at the MRHD) after weaning. The NOAEL for pre- and postnatal development in rats was 5 mg/kg/day, approximately 0.7 times the AUC at the MRHD.

8.2. Lactation

Risk Summary

There are no data on the presence of sparsentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for adverse reactions, such as hypotension in breastfed infants, advise patients not to breastfeed during treatment with FILSPARI.

8.3. Females and Males of Reproductive Potential

Based on data from animal reproductive toxicity studies, FILSPARI may cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy *[see Contraindications (4), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Exclude pregnancy before initiating FILSPARI in females of reproductive potential. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient should discuss the risks to their pregnancy and the fetus.

Contraception

Patients who can become pregnant who are using FILSPARI must use an effective method of contraception prior to initiation of treatment, during treatment, and for two weeks after discontinuation of treatment with FILSPARI to prevent pregnancy *[see Warnings and Precautions (5.3)]*.

8.4. Pediatric Use

The safety and efficacy of FILSPARI in pediatric patients have not been established.

8.5. Geriatric Use

Of the total number of subjects in the PROTECT study of FILSPARI, 15 (7.4%) were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

8.6. Hepatic Impairment

Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C) because of the potential risk of serious liver injury *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

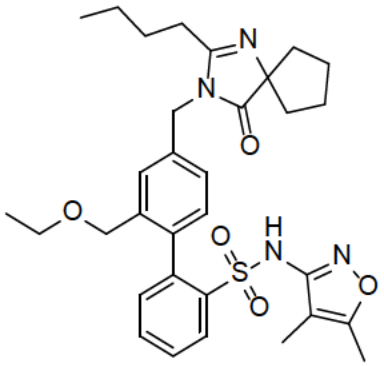
10. OVERDOSAGE

There is no experience with overdose with FILSPARI. Sparsentan has been given in doses up to 1600 mg/day in healthy volunteers, or up to 400 mg/day in IgAN patients. Overdose of FILSPARI may result in decreased blood pressure. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because sparsentan is highly protein-bound.

11. DESCRIPTION

FILSPARI (sparsentan) is an endothelin and angiotensin II receptor antagonist. The chemical name of sparsentan is 2-[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethyl-1,2-oxazol-3-yl)benzenesulfonamide.

Sparsentan is a white to off-white powder, which is practically insoluble in water. Sparsentan has pH-dependent solubility, with intrinsic solubility of 1.48 and 0.055 mg/mL under pH 1.2 and 6.8, respectively. Sparsentan has a molecular weight of 592.76 g/mol, a molecular formula of $C_{32}H_{40}N_4O_5S$, and the following structure:



FILSPARI is available as film-coated 200 mg and 400 mg strength immediate release tablets for oral administration.

The inactive ingredients in FILSPARI are colloidal silicon dioxide, lactose anhydrous, magnesium stearate, silicified microcrystalline cellulose, and sodium starch glycolate. Film-coating is composed of macrogol/polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Sparsentan is a single molecule with antagonism of the endothelin type A receptor (ET_AR) and the angiotensin II type 1 receptor (AT_1R). Sparsentan has high affinity for both the ET_AR (Ki= 12.8 nM) and the AT_1R (Ki=0.36 nM), and greater than 500-fold selectivity for these receptors over the endothelin type B and angiotensin II subtype 2 receptors. Endothelin 1 and angiotensin II are thought to contribute to the pathogenesis of IgAN via the ET_AR and AT_1R, respectively.

12.2. Pharmacodynamics

Dose-response information is not available. At the recommended dose regimen, no statistically significant exposure-response (E-R) relationship was identified between sparsentan exposure and the percentage reduction from baseline in UPCR at Week 36 over the observed sparsentan exposure range. No clinically meaningful E-R relationships were observed for hypotension of any grade and peripheral edema worst grade. A statistically significant relationship was observed between sparsentan exposures and the incidence of hyperkalemia of any grade.

Cardiac Electrophysiology

In a randomized, positive-, and placebo-controlled study in healthy subjects, sparsentan caused QTcF prolongation with maximal mean effect of 8.8 msec (90% CI: 5.9, 11.8) at 800 mg and 8.1 msec (90% CI: 5.2, 11.0) at 1600 mg. The underlying mechanism behind the observed QTc prolongation is unknown but is unlikely to be mediated via direct inhibition of hERG channels. At the recommended dose, no clinically relevant QTc prolongation (i.e., >20 msec) is expected.

12.3. Pharmacokinetics

The pharmacokinetics of sparsentan are presented as geometric mean (% coefficient of variation) unless otherwise specified. The C_{max} and AUC of sparsentan increase less than proportionally following administration of single doses of 200 mg to 1600 mg. Sparsentan showed time-dependent pharmacokinetics which may be related to the drug inducing its own metabolism over time. Steady-state plasma levels are reached within 7 days with no accumulation of exposure at the approved recommended dosage. Following a single oral dose of 400 mg sparsentan, the mean C_{max} and AUC are 7.0 µg/mL and 83.0 µg×h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean C_{max} and AUC are 6.5 µg/mL and 63.6 µg×h/mL, respectively.

Absorption

Following a single oral dose of 400 mg sparsentan, the median (minimum to maximum) time to peak plasma concentration is approximately 3 hours (2 to 8 hours).

Effect of Food

Sparsentan AUC and C_{max} increased by 22% and 108%, respectively, following administration of a single oral 800 mg dose with a high fat, high calorie meal (1000 kcal, 50% fat) *[see Dosage and Administration (2.5)].* No clinically significant differences in sparsentan pharmacokinetics were observed following administration of a single 200 mg dose with a high fat, high calorie meal.

Distribution

The apparent volume of distribution at steady state is 61.4 L at the approved recommended dosage.

Sparsentan is >99% bound to human plasma proteins.

Elimination

The clearance of sparsentan is time-dependent which may be related to the drug inducing its own metabolism over time. The apparent clearance (CL/F) of sparsentan is 3.88 L/h following the initial 400 mg dose then increases to 5.11 L/h at steady state.

The half-life of sparsentan is estimated to be 9.6 hours at steady state.

Metabolism

Cytochrome P450 3A is the major isozyme responsible for the metabolism of sparsentan.

Excretion

After a single dose of radiolabeled sparsentan 400 mg to healthy subjects, approximately 80% of the dose was recovered in feces (9% unchanged) and 2% in urine (negligible amount unchanged). 82% of the dosed radioactivity was recovered within a 10-day collection period.

Specific Populations

No clinically significant differences in the pharmacokinetics of sparsentan were observed based on age (18 – 73 years), sex, race, mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), or mild to moderate hepatic impairment (Child-Pugh class A or B). Patients with severe hepatic impairment (Child-Pugh class C) and eGFR <30 mL/min/1.73 m^2 have not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Other Drugs on Sparsentan

Strong CYP3A inhibitors: Concomitant use with itraconazole (strong CYP3A inhibitor) increased sparsentan C_{max} by 25% and AUC by 174%.

Moderate CYP3A inhibitors: Concomitant use with cyclosporine (moderate CYP3A inhibitor) increased sparsentan C_{max} by 41% and AUC by 70%.

Strong CYP3A inducers: Coadministration of rifampin (strong CYP3A inducer) is predicted to decrease sparsentan C_{max} by 23% and $AUC_{0\text{-}inf}$ by 47% at steady state.

Effect of Sparsentan on Other Drugs

No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A4 substrate) or pitavastatin (OATP1B1, OATP1B3, P-gp, and BCRP substrate) were observed when co-administered with sparsentan. In addition, sparsentan had no clinically significant effect on serum creatinine levels (an endogenous biomarker of OAT2, OCT2, MATE1, and MATE2K) or on 6β-hydroxycortisol (an endogenous biomarker of OAT3).

CYP2B6 substrates: Concomitant use with sparsentan decreased the exposure of bupropion (CYP2B6 substrate) C_{max} by 32% and AUC by 33%.

In Vitro Studies

CYP Enzymes: Sparsentan is a substrate of CYP3A. Sparsentan is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6, CYP2C9, and CYP2C19.

Transporters: Sparsentan is a substrate of P-gp and BCRP but is not a substrate of OATP1B1 or OATP1B3. Sparsentan is an inhibitor of P-gp, BCRP, OATP1B3, and OAT3 but does not inhibit MRP, OATP1B1, NTCP, OCT2, OAT1, MATE1, or MATE2K at relevant concentrations.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: In the two-year rat carcinogenicity study, there was no evidence of increased incidence of neoplasia in male rats orally administered at 15 mg/kg/day (the only dose evaluated) and in female rats orally administered up to 240 mg/kg/day, which provided an exposure approximately 0.7 times and 26 times the AUC at the MRHD, respectively. In the 26-week transgenic mouse study, there was no evidence of increased incidence of neoplasia in male and female mice orally administered sparsentan at doses up to 600 mg/kg/day.

Mutagenesis: There was no evidence of mutagenicity or clastogenicity for sparsentan in in vitro bacteria reverse mutation and chromosomal aberration assays, or in an in vivo rat micronucleus study.

Impairment of fertility: In a fertility and early embryonic development study in rats, oral administration of sparsentan at doses of 20, 80, and 320 mg/kg/day for at least 36 (females) and 49 (males) days did not result in any adverse effects on estrous cycles, mating, fertility, sperm evaluation, or pregnancy incidence at doses up to 320 mg/kg/day, which provided approximately 10 and 14 times the AUC at the MRHD for males and females, respectively. Male reproductive organ toxicity was not evident in chronic toxicity studies with sparsentan at exposures up to 10 times and 1.3 times the AUC at the MRHD in rats and monkeys, respectively.

14. CLINICAL STUDIES

The effect of FILSPARI on proteinuria and kidney function (estimated glomerular filtration rate, eGFR) was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT, NCT03762850) in adults with biopsy-proven primary IgAN, eGFR ≥30 mL/min/1.73 m^2, and total urine protein ≥1.0 g/day on a stable dose of maximally-tolerated RAS inhibitor treatment. Patients with chronic kidney disease due to another condition in addition to IgAN or those who had been recently treated with systemic immunosuppressants were excluded.

Patients were randomized (1:1) to either FILSPARI (400 mg once daily following 200 mg once daily for 14 days) or irbesartan (300 mg once daily following 150 mg once daily for 14 days). Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial. Concomitant use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, other RAS inhibitors, and aldosterone blockers were prohibited.

The primary efficacy endpoint for the interim analysis was the change from baseline in urine protein/creatinine ratio (UPCR) at Week 36 based on the first 281 randomized patients who had reached the Week 36 visit. The key secondary efficacy endpoint for the final analysis was the rate of change in eGFR over a 110-week period following initiation of randomized therapy.

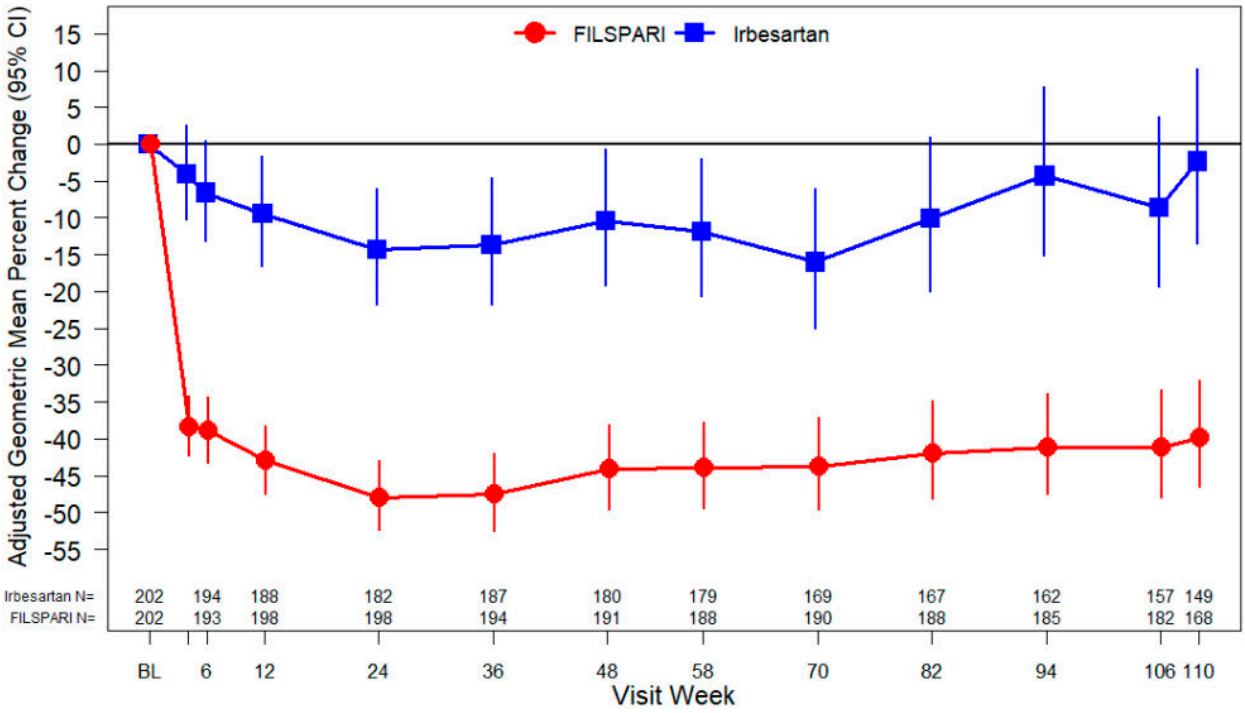
The 404 patients who enrolled and received study medication had a mean age of 46 years (range 18 to 76 years); 70% were male, 67% White, 28% Asian, and 1% Black or African American. Approximately 78% had a history of hypertension, 11% had diabetes or impaired fasting glucose, and 56% had hematuria based on urine dipstick. At baseline, the mean eGFR was 57 mL/min/1.73 m^2, the geometric mean UPCR was 1.2 g/g, and 49 (12%) patients had proteinuria >3.5 g/24 hours.

Urine Protein/Creatinine Ratio (UPCR)

The trial met the prespecified primary endpoint of relative change from baseline in UPCR at Week 36 based on an interim analysis of 281 randomized patients who had reached the Week 36 visit. The interim analysis showed a 45% decrease in UPCR at Week 36 relative to baseline for patients treated with FILSPARI compared to a 15%

decrease for patients treated with irbesartan resulting in a 35% reduction in the ratio of mean UPCR (95% CI: 23% to 45% reduction; p<0.0001). In the final analysis of 404 randomized patients, the treatment effects in UPCR observed at Week 36 and Week 110 were consistent with the results obtained at the interim analysis. The mean percent change from baseline over the course of the double-blind period is displayed in Figure 1.

Figure 1: Geometric Mean Percent Change from Baseline in Urine Protein-to-Creatinine Ratio by Visit through Week 110 (PROTECT, FAS)



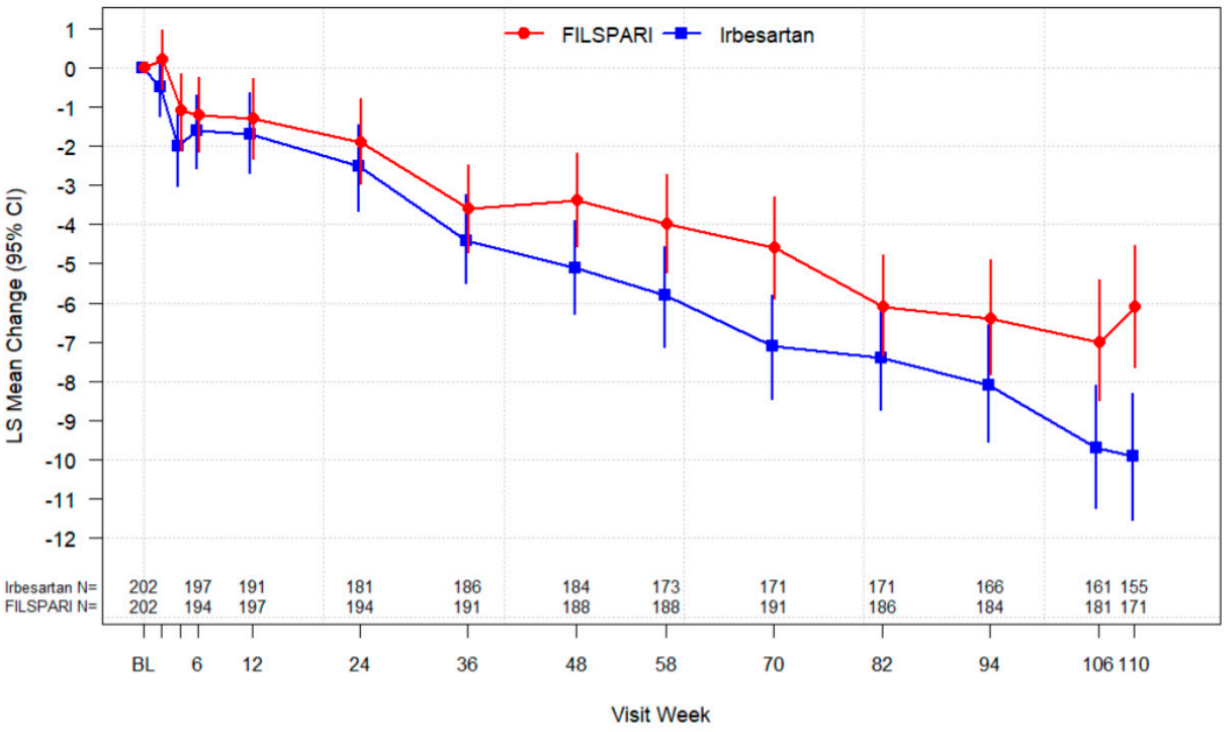
Adjusted GMPC of UPCR was based on MMRM stratified by screening eGFR and total urine protein excretion. MMRM analysis includes UPCR data during the double-blind period up to Week 110 regardless of treatment discontinuation or immunosuppressive therapy initiation. Missing data were imputed using multiple imputation under assumptions of missing at random and missing not at random depending on the patient's intercurrent event status. Baseline was defined as the last non-missing observation on or prior to the start of dosing. Counts in axis table represent number of subjects with observed UPCR data by visit and treatment group. BL=baseline; CI=confidence interval; FAS=full analysis set; GMPC=geometric mean percent change; LS=least squares; MMRM=mixed-model repeated measures; N= number of subjects with available data at the time of analysis; UPCR=urine protein/creatinine ratio.

Estimated Glomerular Filtration Rate (eGFR)

In the final analysis of 404 randomized patients, FILSPARI reduced the rate of decline in kidney function from baseline to Week 110 compared to irbesartan. The mean eGFR slope from baseline to Week 110 was -3.0 mL/min/1.73 m^2 per year for FILSPARI and

-4.2 mL/min/1.73 m^2 per year for irbesartan, corresponding to a treatment effect of 1.2 mL/min/1.73 m^2 per year (95 %CI: 0.2 to 2.1; p=0.0168). The mean change from baseline in eGFR during the double-blind period is shown in Figure 2. The treatment effect on the rate of change in eGFR through Week 110 was generally consistent across key subgroups, including key demographic (such as age, sex, race, ethnicity, and region) and baseline disease (such as baseline BMI and baseline proteinuria) characteristics. The treatment benefit with FILSPARI on the rate of change in eGFR through Week 110 was not evident in patients with an eGFR ≥90 mL/min/1.73 m^2; however, there was a small number of patients in this subgroup.

Figure 2: Absolute Change in eGFR (mL/min/1.73 m^2) by Visit (FAS)



*eGFR was calculated using the CKD-EPI equation. Baseline was defined as the last non-missing observation on or prior to the start of dosing. The analysis includes eGFR data during the double-blind period up to Week 110 regardless of treatment discontinuation or immunosuppressive therapy initiation. Rescue immunosuppressive treatment for IgAN was initiated in 7 (3%) and 18 (9%) patients in the FILSPARI and irbesartan group respectively. BL=baseline; CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; FAS=full analysis set; IgAN=immunoglobulin A nephropathy; LS=least squares; N=number of subjects with available data at the time of analysis.

16. HOW SUPPLIED/STORAGE AND HANDLING

FILSPARI is supplied in bottles of 30 film-coated tablets.

- 200 mg tablets are film-coated, modified oval, white to off-white, debossed with “105” on one side and plain on the other side, available in bottles of 30 tablets with child-resistant caps (NDC 68974-200-30).
- 400 mg tablets are film-coated, modified oval, white to off-white, debossed with “021” on one side and plain on the other side, available in bottles of 30 tablets with child-resistant caps (NDC 68974-400-30).

Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store FILSPARI in its original container.

17. PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Restricted Access

Advise the patient that FILSPARI is only available through a restricted access program called the FILSPARI REMS because of the risk of hepatotoxicity, and that FILSPARI is available only from certified pharmacies that are enrolled in the FILSPARI REMS.

As a component of the FILSPARI REMS, prescribers must review the contents of the FILSPARI Medication Guide with the patient before initiating FILSPARI and patients must sign the FILSPARI REMS Patient Enrollment Form to confirm that they understand the risks of FILSPARI.

Instruct patients of the risk of hepatotoxicity associated with FILSPARI.

Hepatotoxicity

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop taking FILSPARI and seek medical attention *[see Dosage and Administration (2.2, 2.4, 2.6), Warnings and Precautions (5.1)].*

Discuss with the patient the requirement to measure serum aminotransferases every 3 months *[see Dosage and Administration (2.2, 2.6), Warnings and Precautions (5.1, 5.2)].*

Embryo-Fetal Toxicity

Counsel patients who can become pregnant about the need to use effective methods of contraception prior to treatment with FILSPARI, during treatment, and for two weeks after treatment discontinuation. Patients who can become pregnant should have a negative pregnancy test prior to initiation of treatment with FILSPARI *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)].*

Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Lactation

Advise patients not to breastfeed during treatment with FILSPARI *[see Use in Specific Populations (8.2)].*

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medications, over-the-counter drugs, vitamins/supplements, herbal products, and grapefruit *[see Contraindications (4), Warnings and Precautions (5.4, 5.5, 5.6, 5.7), Drug Interactions (7)].*

Other Risks Associated with FILSPARI

Inform patients of other risks associated with FILSPARI, including:

- Hypotension: Advise patients to remain hydrated *[see Warnings and Precautions (5.4)].*
- Hyperkalemia: Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting their healthcare provider *[see Warnings and Precautions (5.6)].*

Dosing

Advise patients to take the full daily dose with water prior to the morning or evening meal. Maintain the same dosing pattern in relationship to meals. If a dose is missed, take the next dose at the regularly scheduled time. Do not take double or extra doses *[see Dosage and Administration (2.5)].*

Distributed by Travere Therapeutics, Inc., San Diego, CA 92130

FILSPARI is a registered trademark of Travere Therapeutics, Inc.

Medication Guide
FILSPARI® (fil spah ree)
(sparsentan)
tablets

What is the most important information I should know about FILSPARI?

FILSPARI can cause serious side effects, including:

- **Liver problems.**
  - **FILSPARI can cause changes in liver tests.** Liver failure was not observed in people treated with FILSPARI in clinical studies, but some medicines that are like FILSPARI can cause liver failure. Your healthcare provider will do blood tests to check your liver before starting treatment with FILSPARI and then every 3 months during treatment. Your healthcare provider may temporarily stop or permanently stop treatment with FILSPARI if you have changes in your liver tests.

    Stop taking FILSPARI and get medical help right away if you develop any of the following signs of liver problems during treatment with FILSPARI:

    - nausea or vomiting
    - pain on the upper right side of your stomach area
    - tiredness
    - loss of appetite
    - yellowing of your skin or the white part of your eyes (jaundice)
    - dark “tea-colored” urine
    - fever
    - itching

    Because of the risk for liver problems, FILSPARI is only available through a restricted access program called the FILSPARI Risk Evaluation and Mitigation Strategy (REMS). Before you begin treatment with FILSPARI, your healthcare prescriber will explain the FILSPARI REMS program, you must read, and agree to all of the requirements of the FILSPARI REMS.
- **Serious birth defects.**

  FILSPARI can cause serious birth defects if taken during pregnancy.
  - **Patients who can become pregnant should not be pregnant when they start taking FILSPARI or become pregnant during treatment with FILSPARI or for two weeks after stopping treatment with FILSPARI.**
  - Patients who can become pregnant should have a negative pregnancy test before starting treatment with FILSPARI.

    Patients who can become pregnant are those who:
    - have entered puberty, even if they have not started their menstrual period, **and**
    - have a uterus, **and**
    - have not gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed.

    Patients who cannot become pregnant are those who:
    - have not yet entered puberty, **or**
    - do not have a uterus, **or**
    - have gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed, **or**
    - are infertile for any other medical reason and this infertility is permanent and cannot be reversed.
  - **Patients who can become pregnant should use effective birth control before starting treatment with FILSPARI, during treatment with FILSPARI, and for two weeks after stopping FILSPARI because the medicine may still be in your body.**
    - Talk with your healthcare provider or gynecologist (a healthcare provider who specializes in reproduction) to find out about options for effective forms of birth control that you may use to prevent pregnancy during treatment with FILSPARI.
    - If you decide that you want to change the form of birth control that you use, talk with your healthcare provider or gynecologist to be sure that you choose another effective form of birth control.
  - **Do not have unprotected sex.** Talk to your healthcare provider or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your healthcare provider may talk with you about using emergency birth control.
  - **Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.**

See “**What are the possible side effects of FILSPARI?**” for more information about side effects.

What is FILSPARI?

FILSPARI is a prescription medicine used to slow kidney function decline in adults with a kidney disease called primary

immunoglobulin A nephropathy (IgAN), who are at risk for their disease getting worse.
It is not known if FILSPARI is safe and effective in children.

Who should not take FILSPARI?

Do not take FILSPARI if you:

- **are pregnant, plan to become pregnant, or become pregnant during treatment with FILSPARI. FILSPARI may cause serious birth defects.** See **"What is the most important information I should know about FILSPARI?"**
- **are taking an angiotensin receptor blocker, endothelin receptor antagonist, or aliskiren.**

Ask your healthcare provider or pharmacist if you are not sure if you take any of these medicines.

Before taking FILSPARI, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- are pregnant or plan to become pregnant during treatment with FILSPARI. FILSPARI may cause serious birth defects. See **"What is the most important information I should know about FILSPARI?"**
- are breastfeeding or plan to breastfeed. It is not known if FILSPARI passes into your breast milk. **Do not** breastfeed during treatment with FILSPARI. Talk to your healthcare provider about the best way to feed your baby during treatment with FILSPARI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and grapefruit. FILSPARI and other medicines may affect each other and cause side effects. **Do not** start any new medicine until you check with your healthcare provider.

Especially tell your healthcare provider if you take:

- nonsteroidal anti-inflammatory drugs (NSAIDs)
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium
- blood pressure medicines
- antacids, including histamine (H2) receptor blocker or proton pump inhibitor (PPI) medicines

Ask your healthcare provider or pharmacist if you are not sure if you take one of these medicines.

How should I take FILSPARI?

- FILSPARI will be provided to you by a certified pharmacy. Your healthcare provider will give you complete details.
- Take FILSPARI exactly as your healthcare provider tells you to take it. **Do not** stop taking FILSPARI unless your healthcare provider tells you.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with FILSPARI if you develop side effects.
- Take FILSPARI whole with water **before** your morning or evening meal. Take your dose **before** the same meal each day.
- If you miss a dose, take the next dose at the regularly scheduled time. **Do not** take 2 doses at the same time or take extra doses.
- If you take an antacid, take FILSPARI 2 hours before or 2 hours after you take your antacid.
- If you take too much FILSPARI, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of FILSPARI?

FILSPARI can cause serious side effects, including:

- **Liver problems.** See **"What is the most important information I should know about FILSPARI?"**
- **Serious birth defects.** See **"What is the most important information I should know about FILSPARI?"**
- **Low blood pressure.** Low blood pressure is common during treatment with FILSPARI and can also be serious. Tell your healthcare provider if you feel dizzy, light-headed, or faint. Stay hydrated during treatment with FILSPARI.
- **Worsening of kidney function.** This is common during treatment with FILSPARI and can also be serious. Your healthcare provider will check your kidney function during treatment with FILSPARI.
- **Increased potassium in your blood.** This is common during treatment with FILSPARI and can also be serious. Your healthcare provider will check your potassium blood level during treatment with FILSPARI.
- **Fluid retention.** FILSPARI can cause your body to hold too much water. Tell your healthcare provider right away if you have any unusual weight gain or swelling of your ankles or legs.

The most common side effects of FILSPARI also include:

- swelling of hands, legs, ankles, and feet (peripheral edema)
- low red blood cells (anemia)
- dizziness

These are not all of the possible side effects of FILSPARI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FILSPARI?

- Store FILSPARI at room temperature between 68°F to 77°F (20°C to 25°C).
- Store FILSPARI in the original container.
- The bottle has a child-resistant closure.

Keep FILSPARI and all medicines out of the reach of children.

General information about the safe and effective use of FILSPARI.

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use FILSPARI for a condition for which it was not prescribed. Do not give FILSPARI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FILSPARI that is written for health professionals.

What are the ingredients in FILSPARI?

Active ingredient: sparsentan

Inactive ingredients: colloidal silicon dioxide, lactose anhydrous, magnesium stearate, silicified microcrystalline cellulose, and sodium starch glycolate. Tablets are film coated with material containing macrogol/polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

Distributed by Travere Therapeutics, Inc., San Diego, CA 92130

For more information, go to www.FILSPARI.com or call 1-877-659-5518.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

REMS

RISK EV A I N MI IG A I S N R A EGY (REMS) D OC EM T
FI SP R® (SP RSN T) REMS

I. A DMINIS R A IVE INF M R I N

Risk: h patotoxicity

Application Numb r: NDA 216403

Application Hold r: Trav r Th rap utics, Inc.

Initial REMS Approval: 02/2023

Most R c nt REMS Updat : 08/2025

II. REMS G O

Th goal of th FILSPARI REMS is to mitigat th risk of h patotoxicity associat d with FILSPARI:

- Obj ctiv 1: Monitor for l vations in liv r nzym s in pati nts xpos d to FILSPARI

III. REMS REQ UIREMEN TS

ravere herapeutics, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe FI SP R must:	
To b com c rtifi d to pr scrib e	1. R vi w th drug's Pr scribing Information. 2. R vi w th following: Pr scrib r and Pharmacy Guid . e 3. Enroll in th REMS by compl ting th Pr scrib r Enrollm nt Form and submitting it to th REMS.
B for tr atm nt e initiation (first dos) e	4. Couns l th pati nt on th risk of h patotoxicity associat d with FILSPARI, th signs and symptoms of liv r probl ms, to contact th e pr scrib r if th pati nt has any signs or symptoms of liv r probl ms, on th REMS r quir m nts including th n d to compl t liv r t sting v ry 3 months during tr atm nt, and that FILSPARI is only availabl through a r strict d distribution program using th Pati nt Guid . 5. Ass ss th pati nt's liv r function. Docum nt and submit to th REMS using th Pati nt Enrollm nt Form. 6. Provid th pati nt with th Pati nt Guid . 7. Enroll th pati nt by compl ting th Pati nt Enrollm nt Form and submitting it to th REMS.
During tr atm nt, e v ry 3 months	8. Ass ss th pati nt's liv r function. 9. Couns l th pati nt on th risk of h patotoxicity if th y ar not complying with th r quir d liv r t sting.
At all tim s e	10. R port adv rs v nts sugg stiv of h patotoxicity to th REMS.

2. Pati t o ar pr crib d FILSPARI:	
Before rea men t ini ia ion (firs dose)	1. Review he Pa ien Guide. 2. Ge a liver es . 3. Receive counseling from he prescriber on he risk of liver problems, he signs and symp oms of liver problems, he need o con ac he prescriber if you have any signs or symp oms of liver problems, and he t need o comple e liver es ing every 3 mon hs during rea men using he Pa ien Guide. 4. Enroll in he REMS by comple ing he Pa ien Enrollmen Form wi h he t prescriber. Enrollmen informa ion will be provided o he REMS. 5. Receive counseling from he pharmacy on he risk of liver problems associa ed wi h FILSPARI rea men .
During rea men , t every 3 mon hs t	6. Ge a liver es . 7. Adhere o he safe use condi ion: Communica e wi h he pharmacy o confirm comple ion of liver es ing. 8. Receive counseling from he pharmacy on he risk of liver problems associa ed wi h FILSPARI rea men .
A all imes t	9. Inform he prescriber if you have any signs or symp oms of liver problems as described in he Pa ien Guide.
3. Outpati t p armaci t at di p FILSPARI mu t:	
To become cer ified o dispense t	1. Designa e an au horized represen a ive o carry ou he cer ifica ion process and oversee implemen a ion and compliance wi h he REMS on behalf of he pharmacy. 2. Have he au horized represen a ive review he Prescriber and Pharmacy Guide. 3. Have he au horized represen a ive cer ify by enrolling in he REMS by comple ing he Ou pa ien Pharmacy Enrollmen Form and submi ing i o he REMS. 4. Train all relevan s aff involved in dispensing on he REMS requiremen s using he Prescriber and Pharmacy Guide. 5. Es ablish processes and procedures o verify he pa ien is enrolled and t he prescriber is cer ified. 6. Es ablish processes and procedures o documen and submi confirma ion of counseling on he risk of hepa o oxici y. 7. Es ablish processes and procedures o verify and documen he pa ien ’s t liver es ing is comple e or he prescriber au horizes he refill.
Before dispensing t	8. Verify he pa ien is enrolled and he prescriber is cer ified hrough he processes and procedures es ablished as a requiremen of he REMS.

Before d e ; at t al d e e, the every 3 mo th q	9. Cou el the at e t o the r k of he atotox c ty. Docume t a d ubmit co f rmat o of cou el throu h the roce e a d rocedure e tabl hed a a re u reme t of the REMS. 10. Ver fy a d docume t the at e t' l ver te t complete or the re cr ber author ze the ref ll throu h the roce e a d rocedure q e tabl hed a a re u reme t of the REMS.
At all t me q	11. D i e e o more tha a 90-day ' u ly. 12. Re ort adver e eve t u e t ve of he atotox c ty to the REMS. 13. Not d tr bute, tra fer, loa , or ell FILSPARI, exce t to cert f ed d e er . 14. Ma ta a d ubmit record of roduct d e to the REMS. 15. Ma ta record that all roce e a d rocedure are lace a d are be followed. 16. Comply w ith aud t carr ed out by Travere Thera eut c , I c. or a th rd arty act o behalf of Travere Thera eut c , I c. to e ure that all roce e a d rocedure are lace a d are be followed.
To ma ta q cert f cat o to q d e e q	17. Have a ew author zed re re e tat ve e roll by complet a d ubmitt a Out at e t Pharmacy E rollme t Form, f the author zed re re e tat ve cha e .
4. Inpatient pharmacies that dispense FILSPARI must:	
Become cert f ed to q d e e q	1. De ate a author zed re re e tat ve to carry out the cert f cat o roce a d over ee mpleme tat o a d compl a ce w ith the REMS o q behalf of the harmacy. 2. Have the author zed re re e tat ve rev ew the Pre cr ber a d Pharmacy Gu de. 3. Have the author zed re re e tat ve cert fy by e roll the REMS by complet the I at e t Pharmacy E rollme t Form a d ubm tt t to the REMS. 4. Tra all releva t taff volved d e o the REMS re u reme t u the Pre cr ber a d Pharmacy Gu de. 5. E tabl h roce e a d rocedure to ver fy a d docume t the at e t e rolled or w ill be e rolled r or to d char e, the at e t u der the care of a cert f ed re cr ber, a d l ver te t complete.
Before d e q	6. Cou el the at e t o the r k of he atotox c ty. Docume t a d ubmit co f rmat o of cou el throu h the roce e a d rocedure e tabl hed a a re u reme t of the REMS. 7. Ver fy a d docume t the at e t e rolled or w ill be e rolled r or to d char e, the at e t u der the care of a cert f ed re cr ber, a d l ver te t complete.
At d char e q	8. D e e o more tha a 30-day ' u ly. q

At all time 9 N		R port adv r v nt ugg tiv of h patotoxicity to th EMS
	10	ot di tribut , tran f r, loan, or ll FILSPA I, xc pt to c rtifi d di p n r
	11	Maintain r cord that all proc and proc dur ar in plac and ar b ing follow ed
	12	Comply with audit carri d out by Trav r Th rap utic , Inc or a third party acting on b half of Trav r Th rap utic , Inc to n ur that all proc and proc dur ar in plac and ar b ing follow ed
To maintain N c rtification to N di p n N	13	Hav a n w authoriz d r pr ntativ nroll by compl ting and ubmitting an Inpati nt Pharmacy Enrollment Form, if th authoriz d r pr ntativ chang
5. Wholesalers-distributors that distribute FILSPARI must:		
To b abl to N di tribut N	1	E tabli h proc and proc dur to n ur that FILSPA I i di tribut d only to c rtifi d pharmaci
	2	Train all r l vant taff involv d in di tribution on th EMS r quir ment
At all time N	3	Di tribut only to c rtifi d pharmaci
	4	Maintain and ubmit r cord of drug di tribution to th EMS
	5	Maintain r cord that all proc and proc dur ar in plac and ar b ing follow ed
	6	Comply with audit carri d out by Trav r Th rap utic , Inc , or a third party acting on b half of Trav r Th rap utic , Inc to n ur that all proc and proc dur ar in plac and ar b ing follow ed

Travere Therapeutics, Inc. must provide training to healthcare providers who prescribe FILSPARI.

Th training includ th following ducational mat rial: Pr crib r and Pharmacy Guid Th training mu t b availabl onlin and hard copy format via fax or mail

Travere Therapeutics, Inc. must provide training to pharmacies that dispense FILSPARI.

Th training includ th following ducational mat rial: Pr crib r and Pharmacy Guid Th training mu t b availabl onlin and hard copy format via fax or mail

To support REMS operations, Travere Therapeutics, Inc. must:

1 Authoriz outpati nt di p n ing ba d on v rifying th pati nt i nroll d and th pr crib r i N c rtifi d

2 E tabli h and maintain a EMS Web it , www.FILSPA I EMS com. Th EMS Web it mu t includ N th capability to compl t pr crib r and inpati nt pharmacy c rtification onlin , th capability to nroll and manag pati nt onlin , and th option to print th Pr cribing Information, M edication Guid , and EMS mat rial All product w eb it for con umer and h althcar provid r mu t includ promin nt EMS- p cific link to th EMS Web it Th EMS Web it mu t not link back to th promotional product w eb it ( )

3. Make e MS Websi e fully opera ional and all MS ma erials available roug e websi e and MS Coordina ing Cen er a e ime IL PA I firs becomes commercially available.

4. Es ablis and main ain a MS Coordina ing Cen er for MS par icipan s a 1-833-513-1325.

5. Es ablis and main ain a valida ed, secure da abase of all MS par icipan s w ho are enrolled and F cer ified in e MS.

6. Ensure prescribers and inpa ien p armacies are able o comple e e cer ifica ion process by fax F and online.

7.F Ensure ou pa ien p armacies are able o comple e e cer ifica ion process by fax.

8.F Ensure prescribersFare able o comple e e pa ien enrollmen process by fax and online.

9. Ensure p armacies are able o verify e pa ien is enrolled and e prescriber is cer ified by p one and online.

10. nsure p armacies are able o enroll as inpa ien (including, bu no limi ed o, p armacies in ospi als, long- erm care facili ies, prisons, and s a e psyc ia ric uni s) or ou pa ien p armacies.

11. No ify prescribers and p armacies of eir MS cer ifica ion wi in one business day.

12. Provide e Prescriber nrollmen orm and e Prescriber and P armacy Guide o prescribers w ho (1) a emp o prescribe IL PA I and are no ye cer ified or (2) inquire abou ow o become cer ified.

13.FProvide cer ified prescribersFaccess o e da abase of cer ified p armacies and enrolled pa ien s.

14. Provide cer ified p armacies access o e da abase of cer ified prescribers and enrolled pa ien s.

To ensure REMS participants' compliance with the REMS, Travere Therapeutics, Inc. must:

15. Verify e name and con ac informa ion of e p armacy's au orized represen a ive every 2 years. If differen an e curren au orized represen a ive on file, e p armacy is required o recer ify wi a new au orized represen a ive.

16. Main ain adequa e records o demons ra e a MS requiremen s ave been me , including, bu no limi ed o records of: IL PA I dis ribu ion and dispensing; cer ifica ion of prescribers and p armacies; enrolled pa ien s; and audi s of MS par icipan s. T ese records mus be readily available for DA inspec ions.

17. s ablis and main ain a plan for addressing non-compliance wi MS requiremen s.

18. Moni or prescribers, p armacies, and w holesaler-dis ribu ors on an ongoing basis o ensure e requiremen s of e MS are being me . Take correc ive ac ion if non-compliance is iden ified, including de-cer ifica ion.

19. Audi all cer ified ou pa ien p armacies and w holesaler-dis ribu ors wi in 180 calendar days af er ey become cer ified o ensure a all MS processes and procedures are in place, func ioning, and suppor e MS requiremen s.

20. Aud u y: 1) cer f ed ou p e ph rmac es, 2) represe ve s mp e of p e ph rmac es h h ve ordered FIL PARI he p s ye r, 3) who es er-d s r bu ors, d 4) he REM Coord g Ce er o e sure h he REM processes d procedures re p ce, fu c o g, d suppor he REM requ reme s.

21. T ke re so b e s eps o mprove oper o s of d comp ce w i h he requ reme s he REM S b sed o mo or g d ev u o of he REMS.

IV. REMS ASSESSMENT TIMETABLE

Tr vere Ther peu cs, I c. mus submi REM Assessme s 12 mo hs, d u y from he d e of he REM pprov (02/17/2023). To f c e c us o of s much forma o s poss b e wh e ow i g re so b e me o prep re he submiss o , he repor g erv covered by e ch ssessme shou d co c ude o e r er h 60 c e d r d ys before he submiss o d e for h ssessme . Tr vere Ther peu cs, I c. mus submi e ch ssessme so h w i be rece ved by he FDA o or before he due d e.

V. REMS MATERIALS

The fo ow i g ma er s re p r of he FIL PARI REM :

Enrollment Forms

Prescr ber:

1. Prescr ber E ro me Form S

P e :

2. P e E ro me Form

Ph rmacy:

3. Ou p e Ph rmacy E ro me Form
4. I p e Ph rmacy E ro me Form

Training and Educational Materials

Prescr ber:

5. Prescr ber d Ph rmacy Gu de

P e :

6. P e Gu de

Ph rmacy:

7. Prescr ber d Ph rmacy Gu de S

Other Materials

8. REM Webs e

VI. STAT T L MENTS

This REMS is required under sec ion 505-1 of he Federal Food, Drug and Cosme ic Ac (FD&C Ac) and consis s of he following elemen s:

1. Elemen s o Assure Safe Use
    - Heal h care providers who prescribe FILSPARI are specially cer ified under 505-1(f)(3)(A). t
    - Pharmacies ha dispense FILSPARI are specially cer ified under 505-1(f)(3)(B).
    - FILSPARI is dispensed o pa ien s wi h evidence or o her documen a ion of safe-use condi ions under 505-1(f)(3)(D).
    - Each pa ien using FILSPARI is subjec o cer ain moni oring under 505-1(f)(3)(E).
2. Implemen a ion Sys em
3. Time able for Submission of Assessmen s t

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing and submitting this **Prescriber Enrollment Form** to the REMS by fax to 1-833-483-4736.
   - Prescriber enrollment can also be completed online at www.FILSPARIREMS.com

Complete all required fields on this form to avoid a delay in the enrollment process.

1 Prescriber Information *(*indicates required field)*

*First Name:	Middle Initial:	*Last Name:	*National Provider Identifier (NPI) #:

*Specialty (select one):
☐ Nephrology ☐ Other (please specify):_____

*Professional Designation (select one):
☐ MD ☐ DO ☐ PA ☐ NP

Office Practice/Clinic Name:

*Address Line #1:	Address Line #2:	
*City:	*State:	*Zip:

Preferred Method of Contact (select one): ☐ Fax ☐ Email *Email:

*Office Phone:	*Fax:	Mobile Phone:

Primary Office Contact Information

First Name:	Last Name:	
Address Line #1:	Address Line #2:	
City:	State:	Zip:

Phone:	Fax:	*Email (required if Office Contact is provided):

Secondary Office Contact Information

First Name:	Last Name:	
Address Line #1:	Address Line #2:	
City:	State:	Zip:

Phone:	Fax:	*Email (required if Office Contact is provided):

2 Prescriber Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

To become certified to prescribe, I must:

- Review the drug's Prescribing Information.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient on the:
  - Risk of hepatotoxicity associated with FILSPARI
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if the patient has any signs or symptoms of liver problems
  - REMS requirements including the need to complete liver testing every 3 months during treatment
  - FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
- Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
- Provide the patient with the **Patient Guide**.
- Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS.

During treatment, every 3 months, I must:

- Assess the patient's liver function.
- Counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the REMS.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI healthcare provider to comply with FILSPARI REMS requirements, and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

*Healthcare Provider Signature:	*Date (MM/DD/YYYY):

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

FILSPARI® REMS PATIENT ENROLLMENT FORM

Instructions:

1. Review the **Patient Guide**.
2. Enroll by completing the **Patient Enrollment Form** with your healthcare provider and submit to the REMS by fax to 1-833-483-4736.
   - Patient enrollment can also be completed with your healthcare provider online at www.FILSPARIREMS.com

Complete all required fields on this form to avoid a delay in the enrollment process.

1 Patient Information *(*indicates required field)*

*First Name:	Middle Initial:	*Last Name:	*Birthdate (MM-DD-YYYY):
*Address Line #1:			Address Line #2:
*City:			*State: *Zip:
*Primary Phone:	Other Phone:		Email:

2 Patient Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

Before treatment initiation (first dose), I must:

- Review the **Patient Guide**.
- Get a liver test.
- Receive counseling from my prescriber on the following using the **Patient Guide**:
  - Risk of liver problems
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if I have any signs or symptoms of liver problems
  - Need to complete liver testing every 3 months during treatment.
- Enroll in the REMS by completing the **Patient Enrollment Form** with my prescriber. Enrollment information will be provided to the REMS.
- Receive counseling from the pharmacy on the risk of liver problems associated with FILSPARI treatment.

During treatment, every 3 months, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of liver testing.
- Receive counseling from the pharmacy on the risk of liver problems associated with FILSPARI treatment.

At all times, I must:

- Inform my prescriber if I have any signs or symptoms of liver problems as described in the **Patient Guide**.

Provide Signature Below

By signing below, I acknowledge the above agreements and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and be stored in a secure and confidential database for the FILSPARI REMS. I understand that I may be contacted by Travere Therapeutics, Inc., and its agents about the FILSPARI REMS for voluntary participation in a research study to evaluate possible liver problems while I am receiving FILSPARI. Participation in the study is not required to be enrolled in the REMS or to receive FILSPARI.

***Patient Signature:**	***Date (MM/DD/YYYY):**
***Parent/Legal Guardian Signature:**	***Date (MM/DD/YYYY):**
Parent/Legal Guardian Name (if signing on behalf of patient):	**Parent/Legal Guardian Email:**

3 Prescriber Information *(*indicates required field)*

*First Name:	*Last Name:
*National Provider Identifier (NPI) #:	

4 Prescriber Authorization *(*indicates required field)*

***For this patient, have you reviewed the results of their current liver testing?**

☐ Yes (if yes, proceed with signing below)
☐ No (if no, necessary testing must be completed before enrolling patient)

Note: Liver testing is required for all patients. Please complete necessary testing before submitting this form.

Provide Signature Below

By signing below, I acknowledge the patient was provided a copy of the **Patient Guide** and was counseled on the following:

- Risk of hepatotoxicity associated with FILSPARI.
- Signs and symptoms of liver problems, and to contact their prescriber if they experience any signs or symptoms of liver problems.
- The REMS requirements including the need to complete liver testing every 3 months during treatment.
- FILSPARI is only available through a restricted distribution program using the **Patient Guide**.

I will continue to fulfill my obligations under the REMS to include assessing the patient's liver function prior to initiation, then every 3 months during treatment.

***Prescriber Signature:**	***Date (MM/DD/YYYY):**

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

FILSPARI® REMS OUTPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing and submitting this **Outpatient Pharmacy Enrollment Form** to the REMS by fax to 1-833-483-4736.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All outpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

Complete all required fields on this form to avoid a delay in the enrollment process.

1. Outpatient Pharmacy Information *(*indicates required field)*

*Outpatient Pharmacy Name:			
*Facility National Provider Identifier (NPI) #:	Drug Enforcement Administration Number (DEA #):		
*Pharmacy Address Line #1:			
Pharmacy Address Line #2:			
*City:		*State:	*Zip:
*Phone:	*Fax:		

Pharmacy Ship To Contact

*First Name:	*Last Name:

Pharmacy Shipping Address, if different from above

*Address Line #1:			
Address Line #2:			
*City:		*State:	*Zip:
*Phone:	*Fax:		

2. Outpatient Pharmacy Authorized Representative Information *(*indicates required field)*

*First Name:	*Last Name:
Position/Title: ☐ Pharmacist ☐ Head of Pharmacy and Therapeutics (P&T) committee ☐ Other (please specify):_____	
*Credentials: ☐ RPh ☐ PharmD ☐ Other	
*Authorized Representative Phone:	*Fax:
*Authorized Representative Email:	*Contact Preference (please select one): ☐ Email ☐ Fax

3. Outpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

- Carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify the patient is enrolled and the prescriber is certified.
- Establish processes and procedures to document and submit confirmation of counseling on the risk of hepatotoxicity.
- Establish processes and procedures to verify and document the patient's liver testing is complete or the prescriber authorizes the refill.

Before dispensing FILSPARI, my pharmacy must:

- Verify the patient is enrolled and the prescriber is certified through the processes and procedures established as a requirement of the REMS.

Before dispensing FILSPARI; at initial dispense, then every 3 months, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient's liver testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS.

At all times, my pharmacy must:

- Dispense no more than a 90-days' supply.
- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain and submit records of product dispensing to the REMS.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Outpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI outpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

*Authorized Representative Signature:	*Date (MM/DD/YYYY):

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS by fax to 1-833-483-4736.
   - Inpatient pharmacy enrollment can also be completed online at www.FILSPARIREMS.com

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

Complete all required fields on this form to avoid a delay in the enrollment process.

1. Inpatient Pharmacy Information *(*indicates required field)*

*Inpatient Pharmacy Name:		
*Inpatient Pharmacy Location: ☐ Hospital ☐ Nursing Home ☐ Hospice ☐ Mental Health Facility ☐ Assisted Living ☐ Prison ☐ Rehabilitation Facility ☐ Other (please specify):_____		
*Facility National Provider Identifier (NPI) #:	Drug Enforcement Administration Number (DEA #):	

Inpatient Pharmacy Address

*Address Line #1:		
Address Line #2:		
*City:	*State:	*Zip:
*Phone:	*Fax:	

Pharmacy Ship To Contact

*First Name:	*Last Name:

Pharmacy Shipping Address, if different from above

*Address Line #1:		
Address Line #2:		
*City:	*State:	*Zip:
*Phone:	*Fax:	

2. Inpatient Pharmacy Authorized Representative Information *(*indicates required field)*

* First Name:	Position/Title: ☐ Hospital pharmacist ☐ Head of Pharmacy and Therapeutics (P&T) committee ☐ Other (please specify):
* Last Name:	
*Authorized Representative Office Phone:	*Fax:
*Authorized Representative Email:	*Contact Preference (select one): ☐ Email ☐ Fax

3. Inpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

- Carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

Before dispensing FILSPARI, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

At discharge, my pharmacy must:

- Dispense no more than a 30-days' supply.

At all times, my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI inpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

*Authorized Representative Signature:	*Date (MM/DD/YYYY):

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

FILSPARI® REMS

PRESCRIBER AND PHARMACY GUIDE

FILSPARI®
(sparsentan) tablets 200 mg/400 mg

TABLE E T

FILSPARI R S

I I ATIO N

FILSPARI is indicated to slow kidney function decline in adults with rimary immunoglobulin A ne hro athy (IgA) who are at risk for disease rogression.

RISK OF H PATOTOXI ITY

Some ndothelin Rece tor Antagonists (RAs) have caused elevations of aminotransferases, he atotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the U er Limit of ormal (UL) have been observed in u to 3.5% of FILSPARI-treated atients, including cases confirmed with rechallenge.

Initiate treatment with FILSPARI only after measuring aminotransferase levels and total bilirubin. Avoid initiation in atients with elevated aminotransferases (>3x UL) because monitoring for he atotoxicity in these atients may be more difficult and these atients may be at increased risk for serious he atotoxicity. p

asure aminotransferase levels and total bilirubin rior to initiation of FILSPARI then every 3 months during treatment with FILSPARI.

FILSPARI R S OV RVI W

ue to the risk of he atotoxicity, FILSPARI is only available to atients through a restricted distribution rogram under an F A-required R , called the FILSPARI R . S

The goal of the FILSPARI R is to S mitigate the risk of he atotoxicity associated with FILSPARI:

- Objective 1: nitor for elevations in liver enzymes in atients ex osed to FILSPARI

FILSPARI R S R QUIR M NTS

- Prescribers must be certified in the FILSPARI R S and com ly with the S requirements to rescribe FILSPARI
- Pharmacies must be certified in the FILSPARI R S and com ly with the S requirements to dis ense FILSPARI
- Patients must enroll in the FILSPARI R to S ceive FILSPARI
  - Patients must com ly with liver testing requirements to receive FILSPARI
- Prescribers must educate and counsel atients on the risk of he atotoxicity associated with FILSPARI using the **Patient Guide**
- Prescribers must assess liver function for atients rior to initiation of FILSPARI then every 3 months during treatment to receive FILSPARI
- Prescribers must re ort any adverse events suggestive of he atotoxicity to the FILSPARI R S

ROLE OF PRES R ERS

P sc ib s must compl t th following st ps to p sc ib F LSPAR :

1 Read the FILSPARI Prescribing Information and the Prescriber and Pharmacy Guide to understand the FILSPARI REMS and the risk of hepatotoxicity associated with FILSPARI

2 Complete the Prescriber Enrollment Form

- P sc ib s will att st to und standing th isk of h patotoxicity associat d with F LSPAR and ag to comply with th qui m ents of th F LSPAR REMS
- ompl t th fo m onlin at www.F LSPAR REMS.com o fax th compl t d fo m to 1-833-483-4736

3 Assess liver function

- O d and vi w liv t st sults:
  - P io to initiating t atm ent
  - Ev y 3 months du ing t atm ent

Th pati nt must ag to b contact d by th c tifi d pha macy p io to ach shipm nt. Th c tifi d pha macy will confi m th pati nt has compl t d th i liv t sting.

4 Educate/counsel patients about the risk of hepatotoxicity associated with FILSPARI and about the FILSPARI REMS

- R vi w and p ovid th **Patient Guide** p io to initiating t atm ent
- ouns l th pati nt about:
  - Th isk of h patotoxicity, th signs and symptoms of liv p obl ms, th n d to contact th p sc ib if th pati nt has any signs o symptoms of liv p obl ms, and on th REMS qui m ents including th n d to compl t liv t sting v y 3 months du ing t atm ent
  - F LSPAR is only availabl th ough a st ict d dist ibution p og am call d th F LSPAR REMS
- ouns l any pati nt who is not complying with th qui d liv t sting

5 Enroll patients into the FILSPARI REMS

- ompl t and submit th **Patient Enrollment Form** onlin at www.F LSPAR REMS.com o via fax to 1-833-483-4736

At all times, prescribers must:

- Notify th F LSPAR REMS of any adv s v nt sugg stiv of h patotoxicity by calling 1-833-513-1325

Reference ID: 5649655 .

OUTPATIENT PHARMACY DISPENSING

Only a limited number of certified pharmacies will dispense F LS R for outpatients. ll outpatient pharmacies that wish to stock F LS R must contract with Travere Therapeutics, nc.

To become certified to dispense FILSPARI, an outpatient pharmacy must:

- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy
- Have the authorized representative review the **Prescriber and Pharmacy Guide**
- Have the authorized representative certify by enrolling in the REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**
- Establish processes and procedures to verify the patient is enrolled and the prescriber is certified
- Establish processes and procedures to document and submit confirmation of counseling on the risk of hepatotoxicity
- Establish processes and procedures to verify and document the patient's liver testing is complete or the prescriber authorizes the refill

Before dispensing FILSPARI, the outpatient pharmacy must:

- Verify the patient is enrolled and the prescriber is certified through the processes and procedures established as a requirement of the REMS
  - Outpatient pharmacies can verify by contacting the F LS R REMS online at www.F LS R REMS.com or by phone at 1-833-513-1325

Before dispensing FILSPARI; at initial dispense, then every 3 months, the outpatient pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. ocument and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS
  - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing
- Verify and document the patient's liver testing is complete or the prescriber authorizes the refill : through the processes and procedures established as a requirement of the REMS

Reference ID: 5649655 :

ROLE OF CERT F E RM AC ES continued

At all times the outpatient pharmacy must:

- Dispense no more than a 90-days' supply
  - certified prescriber may be eligible to provide the outpatient pharmacy a one-time authorization to dispense a greater than 90-days' supply. The outpatient pharmacy must report the reason to the F LS R REMS. For information on the eligibility to dispense more than a 90-days' supply and related authorization process, contact the F LS R REMS at 1-833-513-1325
- Report adverse events suggestive of hepatotoxicity to the REMS at 1-833-513-1325
- Not distribute, transfer, loan, or sell F LS R , except to certified dispensers
- Maintain and submit records of product dispensing to the REMS
- Maintain records that all processes and procedures are in place and being followed
- Comply with audits carried out by Travere Therapeutics, nc. or a third party acting on behalf of Travere Therapeutics, nc. to ensure that all processes and procedures are in place and are being followed

To maintain certification to dispense the outpatient pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Outpatient Pharmacy Enrollment Form**, if the authorized representative changes

INPATIENT PHARMACY DISPENSING:

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the F LS R REMS may stock F LS R for patients being treated in the inpatient setting.

To become certified to dispense FILSPARI an inpatient pharmacy must:

- Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy
- Have the authorized representative review the **Prescriber and Pharmacy Guide**
- Have the authorized representative certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete

Before dispensing FILSPARI the inpatient pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. ocument and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS
  - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete
  - Liver testing will be required every 3 months during treatment

ROLE OF CERT F E RM AC ES continued

At discha ge, the inpatient pha macy must:

- Dispense no more than a 30-days' supply

At all times, the inpatient pha macy must:

- Report adverse events suggestive of hepatotoxicity to the REMS
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers
- Maintain records that all processes and procedures are in place and are being followed
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed

To maintain ce tification to dispense, the inpatient pha macy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pha macy En ollment Fo m**, if the authorized representative changes

For a list of Certified Pharmacies, call the FILSPARI REMS at 1-833-483-4736.

THE FILS M S E OORDIN TING ENTE

- Enters every FILSP RI certified prescriber, enrolled patient, and enrolled pharmacy into the FILSP RI REMS database
- Collects all **Patient Enrollment Forms**, **Prescriber Enrollment Forms**, and **Pharmacy Enrollment Forms (Outpatient and Inpatient)**
- llows access to the FILSP RI REMS database to the certified pharmacies for verification of A patient and prescriber information

Notes A

Reference ID: 5649655 A

ADDITIONAL QUESTIONS

Please visit www.FILSPARIREMS.com or call the FILSPARI REMS at 1-833-513-1325 for more information about the FILSPARI REMS.

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events, or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Phone: 1-833-513-1325
www.FILSPARIREMS.com
Fax: 1-833-483-4736

FILSPARI®
(sparsentan) tablets
200 mg/400 mg

Approval: MM/2025

FILSPARI® REMS

PATIENT GUIDE

Reference ID: 5649655

TABLE OF CONTENTS

INFORMATION FOR ATI NT

WH AT I FIL ARI?

FIL ARI is a prescription medicine used to slow idney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at ris for disease progression.

AT I TH RIOU RI K OF FIL ARI?

FILSPARI can cause liver problems. atients must have their liver function chec ed before starting k FIL ARI then every 3 months during treatment with FIL ARI.

AT I TH FIL ARI RI K VALUATION AND MITIGATION TRAT GY (R M S)?

Because of the ris of liver problems, the Food and Drug Administration (FDA) has required a program called a Ris valuation and Mitigation trategy (R M S) for FIL ARI. The purpose of the FIL ARI R M S is to ma e sure the benefits of FIL ARI outweigh the ris s. atients must enroll in the FIL ARI R M S to receive FIL ARI. k

Reference ID: 5649655 k

HOW DO I ENROLL AND STAY IN THE FILSPARI REMS?

- Read the patient information about FILSPARI and the FILSPARI REMS included in this guide or on the **REMS Website**, www.FILSPARIREMS.com
- Talk with your prescriber to ensure the benefits outweigh the risks of FILSPARI
- Ask questions. Make sure you understand the benefits and risks and what you need to do to enroll and take part in the FILSPARI REMS. Make sure you know how to receive and take FILSPARI
- Before starting FILSPARI: b
  - Get a liver test
- During treatment:
  - Get a liver test every 3 months
- You and your prescriber need to choose a certified pharmacy to supply FILSPARI. In some cases, your insurance company may need you to use a specific certified pharmacy
- You and your prescriber must fill out the **Patient Enrollment Form**. fter you read and sign it, your prescriber will send it to the FILSPARI REMS
- Your prescription will e mailed to you from a certified pharmacy

WHERE THE FILSPARI REMS REQUIREMENTS FORME?

o receive FILSPARI, you must:

- Talk to your prescriber to ensure the benefits outweigh the risks of FILSPARI
- Get a liver test efore starting FILSPARI then every 3 months during treatment
- Receive counseling from your prescriber on the risk of liver problems using the **Patient Guide**
- Enroll in the FILSPARI REMS by completing and signing the **Patient Enrollment Form**
- **Be sure you get your liver test every 3 months during treatment. Your certified pharmacy will call you every 3 months to provide counseling and confirm completion of a liver test before shipping your refill. If you do not get your liver test, you may not receive your FILSPARI on time**

Reference ID: 5649655 b

HOW WILL I RECEIVE MY FILSPARI?

Only pharmacies that are certified in the FILSPARI REMS can provide FILSPARI to you. In some cases, your insurance company may require you to use a specific certified pharmacy.

Your certified pharmacy ships your FILSPARI refill to you. The certified pharmacy will confirm that you have completed a liver test (every 3 months during treatment) before refilling your prescription. **It is important that your certified pharmacy is able to contact you in order to avoid delays in your refills.**

REMINDERS

- **Get a liver test before starting FILSPARI then every 3 months during treatment**
- **Tell the certified pharmacy when they call whether you completed your liver test**
- **Tell your healthcare provider right away if you have any of these symptoms of liver problems while taking FILSPARI:**
  - **Nausea**
  - **Vomiting**
  - **Pain on the upper right side of your stomach area**
  - **Tiredness**
  - **Loss of appetite**
  - **Yellowing of the skin or the whites of your eyes (jaundice)**
  - **Dark "tea-colored" urine**
  - **Fever**
  - **Itching**

If you have questions or concerns about FILSPARI, talk to your healthcare provider. Please visit **www.FILSPARIREMS.com** or call **1-833-513-1325** Monday through Friday from 8 AM EST to 8 PM EST for more information about the FILSPARI REMS.

Approval: MM/2025

Phone: 1-833-513-1325 www.FILSPARIREMS.com Fax: 1-833-483-4736

THE FILSPARI® REMS (RISK EVALUATION AND MITIGATION STRATEGY)

The FILSPARI REMS is a safety program that manages the risk of liver problems when taking FILSPARI. The FILSPARI REMS is required by the Food and Drug Administration (FDA).

The goal of the FILSPARI REMS is to mitigate the risk of hepatotoxicity associated with FILSPARI:

- Objective 1: Monitor for elevations in liver enzymes in patients exposed to FILSPARI

Prescribers

Click here to learn how to prescribe FILSPARI

To prescribe FILSPARI:

1. **Review** the Prescribing Information and **Prescriber and Pharmacy Guide**
2. **Certify** by enrolling in the FILSPARI REMS by completing the **Prescriber Enrollment Form** and submitting it to the FILSPARI REMS
3. **Counsel** patients on the risk of hepatotoxicity associated with FILSPARI using the **Patient Guide**
4. **Assess** the patient's liver function
5. **Enroll** patients in the FILSPARI REMS by completing and submitting the **Patient Enrollment Form** to the FILSPARI REMS
6. **Monitor** patients based on REMS requirements

Resources for Prescribers

- Prescriber and Pharmacy Guide
- Prescriber Enrollment Form
- Patient Enrollment Form: English, Spanish, Chinese
- Patient Guide: English, Spanish, Chinese

Patients

Click here to learn how to receive FILSPARI

To receive FILSPARI:

1. **Review** the **Patient Guide**
2. **Get** a liver test prior to initiating FILSPARI then every 3 months during treatment
3. **Receive** counseling at treatment initiation and then every 3 months to understand the risk of liver problems associated with FILSPARI
4. **Enroll** in the FILSPARI REMS by completing the **Patient Enrollment Form** with your prescriber

Resources for Patients

- Patient Guide: English, Spanish, Chinese

Outpatient Pharmacies

Click here to learn how to dispense FILSPARI

To dispense FILSPARI:

1. **Designate** an authorized representative to carry out the certification process and oversee implementation and compliance with the FILSPARI REMS on behalf of the pharmacy
2. **Have** the authorized representative review the **Prescriber and Pharmacy Guide**
3. **Have** the authorized representative certify by enrolling in the FILSPARI REMS by completing the **Outpatient Pharmacy Enrollment Form**, and submitting it to the FILSPARI REMS
4. **Train** staff involved in dispensing FILSPARI and comply with REMS requirements
5. **Before dispensing**:
   - **Contact** the FILSPARI REMS online or by phone to verify the patient is enrolled in the FILSPARI REMS and the prescriber is certified
6. **Before dispensing; at initial dispense, then every 3 months:**
   - **Counsel** the patient on the risk of hepatotoxicity associated with FILSPARI
   - **Verify** and document the patient's liver testing is complete or the prescriber authorizes the refill
7. **Dispense** no more than a 90-days' supply
8. **Provide** dispensing data to the FILSPARI REMS

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide: English, Spanish, Chinese

Inpatient Pharmacies

Click here to learn how to dispense FILSPARI

To dispense FILSPARI:

1. **Designate** an authorized representative to carry out the certification process and oversee implementation and compliance with the FILSPARI REMS on behalf of the pharmacy
2. **Have** the authorized representative review the **Prescriber and Pharmacy Guide**
3. **Have** the authorized representative certify by enrolling in the FILSPARI REMS by completing the **Inpatient Pharmacy Enrollment Form**, and submitting it to the FILSPARI REMS
4. **Train** staff involved in dispensing FILSPARI and comply with REMS requirements
5. **Before dispensing**:
   - **Counsel** the patient on the risk of hepatotoxicity associated with FILSPARI
   - **Verify** and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete
6. **Dispense** no more than a 30-days' supply at discharge

Resources for Inpatient Pharmacies

- Prescriber and Pharmacy Guide
- Inpatient Pharmacy Enrollment Form
- Patient Guide: English, Spanish, Chinese

To learn more about the serious risk of hepatotoxicity associated with FILSPARI, please refer to the **US Prescribing Information including Boxed Warning**, the **Prescriber and Pharmacy Guide** and the **Patient Guide**.

Prescribers

Only prescribers certified by the FILSPARI REMS can prescribe FILSPARI and only pharmacies certified by the FILSPARI REMS can dispense FILSPARI to patients.

Patients must be enrolled in the FILSPARI REMS and follow all the safety rules in the FILSPARI REMS in order to receive FILSPARI.

Prescriber Requirements

How do I become certified in the FILSPARI REMS?

1. Review the following educational materials to understand the FILSPARI REMS and the risk of hepatotoxicity associated with FILSPARI:
   - **Prescribing Information**
   - **Prescriber and Pharmacy Guide**
2. Complete and submit the **Prescriber Enrollment Form:**
   - **Online**
   - **By fax**

How do I enroll my patient in the FILSPARI REMS and what steps should I take prior to treatment initiation?

1. Counsel the patient on the risk of hepatotoxicity associated with FILSPARI, the signs and symptoms of liver problems, to contact the prescriber if the patient has any signs or symptoms of liver problems, on the REMS requirements including the need to complete liver testing every 3 months during treatment, and that FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
2. Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
3. Provide the patient with the **Patient Guide**.
4. Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS:
   - **Online**
   - **By fax**

Once a patient is on FILSPARI, how often should I monitor my patient?

- Assess the patient's liver function every 3 months during treatment.
- Report any adverse events suggestive of hepatotoxicity to the REMS.

PDFs for Download

Resources for Prescribers

- **Prescriber and Pharmacy Guide**
- **Prescriber Enrollment Form**
- Patient Enrollment Form
  - English
  - Spanish
  - Chinese
- Patient Guide
  - English
  - Spanish
  - Chinese

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

CONTINUE

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

1234567890 CONTINUE

*First Name | Middle Initial | *Last Name

*Specialty (select one)
- ○ Nephrology
- ○ Other (please specify)

*Professional Designation (select one)
- ○ MD ○ DO ○ PA ○ NP

Office Practice/Clinic Name

*Address Line #1 | Address Line #2

*City | *State | *Zip

*State: -- Please Select --

Preferred Method of Contact (select one)
- ○ Fax ○ Email

*Email | *Office Phone | *Fax | Mobile Phone

Primary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

State: -- Please Select --

Email | Phone | Fax

Secondary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

State: -- Please Select --

Email | Phone | Fax

2 Prescriber Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

To become certified to prescribe, I must:

- Review the drug's Prescribing Information.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient on the:
  - Risk of hepatotoxicity associated with FILSPARI
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if the patient has any signs or symptoms of liver problems
  - REMS requirements including the need to complete liver testing every 3 months during treatment
  - FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
- Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
- Provide the patient with the **Patient Guide**.
- Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS.

During treatment, every 3 months, I must:

- Assess the patient's liver function.
- Counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the REMS.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI healthcare provider to comply with FILSPARI REMS requirements, and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Healthcare Provider Signature

CLEAR | CANCEL | SUBMIT

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

1234567890 CONTINUE

*First Name | Middle Initial | *Last Name

*Specialty (select one)
- ○ Nephrology
- ◉ Other (please specify)

*Professional Designation (select one)
- ○ MD ○ DO ○ PA ○ NP

*Other Specialty

Other

Office Practice/Clinic Name

*Address Line #1 | Address Line #2

*City | *State | *Zip

-- Please Select --

Preferred Method of Contact (select one)
- ○ Fax ○ Email

*Email | *Office Phone | *Fax | Mobile Phone

Primary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

-- Please Select --

Email | Phone | Fax

Secondary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

-- Please Select --

Email | Phone | Fax

2 Prescriber Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

To become certified to prescribe, I must:

- Review the drug's Prescribing Information.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient on the:
  - Risk of hepatotoxicity associated with FILSPARI
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if the patient has any signs or symptoms of liver problems
  - REMS requirements including the need to complete liver testing every 3 months during treatment
  - FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
- Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
- Provide the patient with the **Patient Guide**.
- Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS.

During treatment, every 3 months, I must:

- Assess the patient's liver function.
- Counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the REMS.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI healthcare provider to comply with FILSPARI REMS requirements, and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Healthcare Provider Signature

CLEAR | CANCEL | SUBMIT

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Prescriber Enrollment Submitted Successfully

Thank you for submitting your information to enroll in the FILSPARI REMS.

A confirmation of this submission has been sent to the email address provided. This email will also include instructions on how to create your web account for the FILSPARI REMS.

If you do not receive the email within the next few hours or would like to update your enrollment information at any time, please contact the FILSPARI REMS for assistance at 1-833-513-1325.

Patients

What is FILSPARI?

FILSPARI is a prescription medicine used to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

What is the serious risk of FILSPARI?

FILSPARI can cause liver problems. Patients must have their liver function checked before starting FILSPARI then every 3 months during treatment with FILSPARI.

How do I become enrolled in the FILSPARI REMS?

1. **Read** the **Patient Guide**.
2. **Review** and discuss the benefits and risks associated with FILSPARI with your prescriber.
3. **Enroll** in the FILSPARI REMS by completing the **Patient Enrollment Form** with your prescriber.

Please refer to the details provided below and in the **Patient Guide** for REMS requirements.

What are the FILSPARI REMS requirements for me?

To receive FILSPARI, you must:

- Talk to your prescriber to ensure the benefits outweigh the risks of FILSPARI.
- Receive counseling from your prescriber on the risk of liver problems using the **Patient Guide**.
- Enroll in the FILSPARI REMS by completing and signing the **Patient Enrollment Form**.
- Get a liver test before starting FILSPARI then every 3 months during treatment.
- **Be sure you get your liver test every 3 months during treatment. Your certified pharmacy will call you every 3 months to provide counseling and confirm completion of a liver test before shipping your refill. If you do not get your liver test, you may not receive your FILSPARI on time.**

How will I receive my FILSPARI?

Only pharmacies that are certified in the FILSPARI REMS can provide FILSPARI to you. In some cases, your insurance company may require you to use a specific certified pharmacy.

Your certified pharmacy ships your FILSPARI refill to you. The certified pharmacy will confirm that you have completed a liver test (every 3 months during treatment) before refilling your prescription. **It is important that your certified pharmacy is able to contact you in order to avoid delays in your refills**.

If you have questions or concerns about FILSPARI, talk to your prescriber. Please visit **www.FILSPARIREMS.com** or call **1-833-513-1325** for more information about the FILSPARI REMS.

PDFs for Download

Resources for Patients

Patient Guide
English
Spanish
Chinese

Outpatient Pharmacies

Only a limited number of certified pharmacies will dispense FILSPARI for outpatients. All outpatient pharmacies that wish to stock FILSPARI must contract with Travere Therapeutics, Inc., and must have the authorized representative certify by enrolling in the FILSPARI REMS.

Contact the FILSPARI REMS to obtain contact information for certified outpatient pharmacies and distributors who are authorized to ship to certified outpatient pharmacies.

To become certified to dispense FILSPARI, outpatient pharmacies must:

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
2. Have the authorized representative review the **Prescriber and Pharmacy Guide**.
3. Have the authorized representative certify by enrolling in the REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS:
   - **By fax**
4. Train all relevant staff involved in dispensing on REMS requirements using the **Prescriber and Pharmacy Guide**.
5. Establish processes and procedures to verify the patient is enrolled and the prescriber is certified.
6. Establish processes and procedures to document and submit confirmation of counseling on the risk of hepatotoxicity.
7. Establish processes and procedures to verify and document the patient's liver testing is complete or the prescriber authorizes the refill.

To ensure compliance with FILSPARI REMS requirements, outpatient pharmacies must:

1. Before dispensing FILSPARI, the outpatient pharmacy must:
   - **Verify** the patient is enrolled and the prescriber is certified through the processes and procedures established as a requirement of the REMS.
2. Before dispensing FILSPARI; at initial dispense, then every 3 months, the outpatient pharmacy must:
   - **Counsel** the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
     - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing.
   - **Verify** and document the patient's liver testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS.
3. At all times, the outpatient pharmacy must:
   - **Dispense** no more than a 90-days' supply.
     - A certified prescriber may be eligible to provide the outpatient pharmacy a one-time authorization to dispense a greater than 90-days' supply. The outpatient pharmacy must report the reason to the FILSPARI REMS. For information on the eligibility to dispense more than a 90-days' supply and related authorization process, contact the FILSPARI REMS at 1-833-513-1325.
   - **Report** adverse events suggestive of hepatotoxicity to the REMS.
   - **Not** distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
   - **Maintain** and submit records of product dispensing data to the REMS.
   - **Maintain** records that all processes and procedures are in place and are being followed.
   - **Comply** with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and being followed.
4. To maintain certification to dispense, the outpatient pharmacy must:
   - **Have a new authorized representative enroll by completing and submitting** an **Outpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Contact the FILSPARI REMS at 1-833-513-1325 for more information on becoming a certified outpatient pharmacy.

Login is available for certified pharmacies.

PDFs for Download

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Inpatient Pharmacies

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the FILSPARI REMS may stock FILSPARI for patients being treated in the inpatient setting.

Contact the FILSPARI REMS to obtain contact information for certified inpatient pharmacies and distributors who are authorized to ship to certified inpatient pharmacies.

To become certified to dispense FILSPARI, inpatient pharmacies must:

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
2. Have the authorized representative review the **Prescriber and Pharmacy Guide**.
3. Have the authorized representative certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS:
   - **Online**
   - **By fax**
4. Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
5. Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

To ensure compliance with FILSPARI REMS requirements, inpatient pharmacies must:

1. Before dispensing FILSPARI, the inpatient pharmacy must:
   - **Counsel** the patient on the risk of hepatoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
     - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing.
   - **Verify** and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete by contacting the FILSPARI REMS **online** or by phone at 1-833-513-1325.
     - Liver testing will be required every 3 months during treatment.
2. At discharge, the inpatient pharmacy must:
   - **Dispense** no more than a 30-days' supply.
3. At all times, the inpatient pharmacy must:
   - **Report** adverse events suggestive of hepatotoxicity to the REMS.
   - **Not** distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
   - **Maintain** records that all processes and procedures are in place and are being followed.
   - **Comply** with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and being followed.
4. To maintain certification to dispense, the inpatient pharmacy must:
   - **Have a new authorized representative enroll by completing and submitting** an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Login is available for certified pharmacies.

PDFs for Download

Resources for Inpatient Pharmacies

Prescriber and Pharmacy Guide

Inpatient Pharmacy Enrollment Form

Patient Guide
English
Spanish
Chinese

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

CONTINUE

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

1234567890

*Inpatient Pharmacy Name

*Inpatient Pharmacy Location

○ Hospital ○ Nursing Home ○ Hospice ○ Mental Health Facility
○ Assisted Living ○ Prison ○ Rehabilitation Facility ○ Other (please specify)

Drug Enforcement Administration Number (DEA #)

Inpatient Pharmacy Address

*Address Line #1 | Address Line #2

*City | *State (-- Please Select --) | *Zip

*Phone | *Fax

Pharmacy Ship To Contact

*First Name | *Last Name

Pharmacy Shipping Address

☐ Pharmacy Shipping Address - Same as above

*Address Line #1 | Address Line #2

*City | *State (-- Please Select --) | *Zip

*Phone | *Fax

2 Inpatient Pharmacy Authorized Representative Information

*First Name | *Last Name

Position/Title:

○ Hospital pharmacist ○ Head of Pharmacy and Therapeutics (P&T) committee
○ Other (please specify)

*Authorized Representative Office Phone | *Fax | *Authorized Representative Email

*Contact Preference (select one):

○ Email ○ Fax

3 Inpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

- Carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

Before dispensing FILSPARI, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

At discharge, my pharmacy must:

- Dispense no more than a 30-days' supply.

At all times, my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI inpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Authorized Representative Signature

CLEAR | CANCEL | SUBMIT

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

1234567890

*Inpatient Pharmacy Name

*Inpatient Pharmacy Location

○ Hospital ○ Nursing Home ○ Hospice ○ Mental Health Facility
○ Assisted Living ○ Prison ○ Rehabilitation Facility ◉ Other (please specify)

Drug Enforcement Administration Number (DEA #)

*Other Inpatient Pharmacy Location

Other

Inpatient Pharmacy Address

*Address Line #1

Address Line #2

*City

*State

-- Please Select --

*Zip

*Phone

*Fax

Pharmacy Ship To Contact

*First Name

*Last Name

Pharmacy Shipping Address

☑ Pharmacy Shipping Address - Same as above

2 Inpatient Pharmacy Authorized Representative Information

*First Name

*Last Name

Position/Title:

○ Hospital pharmacist ○ Head of Pharmacy and Therapeutics (P&T) committee
◉ Other (please specify)

*Other Position/Title

Please Specify

*Authorized Representative Office Phone

*Fax

*Authorized Representative Email

*Contact Preference (select one):

○ Email ○ Fax

3 Inpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

- Carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

Before dispensing FILSPARI, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

At discharge, my pharmacy must:

- Dispense no more than a 30-days' supply.

At all times, my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI inpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Authorized Representative Signature

CLEAR | CANCEL | SUBMIT

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

Inpatient Pharmacy Enrollment Submitted Successfully

Thank you for submitting your information to enroll in the FILSPARI REMS.

A confirmation of this submission has been sent to the email address provided. This email will also include instructions on how to create your web account for the FILSPARI REMS.

If you do not receive the email within the next few hours or would like to update your enrollment information at any time, please contact the FILSPARI REMS for assistance at 1-833-513-1325.

Resources

Resources for Prescribers

- Prescriber and Pharmacy Guide
- Prescriber Enrollment Form
- Patient Enrollment Form
  - English
  - Spanish
  - Chinese
- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Patients

- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Inpatient Pharmacies

- Prescriber and Pharmacy Guide
- Inpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Contact Us

Phone

1-833-513-1325

Fax

1-833-483-4736

Hours of Operation

Monday - Friday
8:00 AM - 8:00 PM
EST

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325.

Report all other suspected adverse events, or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or FDA at 1-800-FDA-1088 or online at **www.fda.gov/medwatch**.

For FILSPARI REMS information contact:
Phone: 1-833-513-1325
Fax: 1-833-483-4736

Certified Outpatient Pharmacies

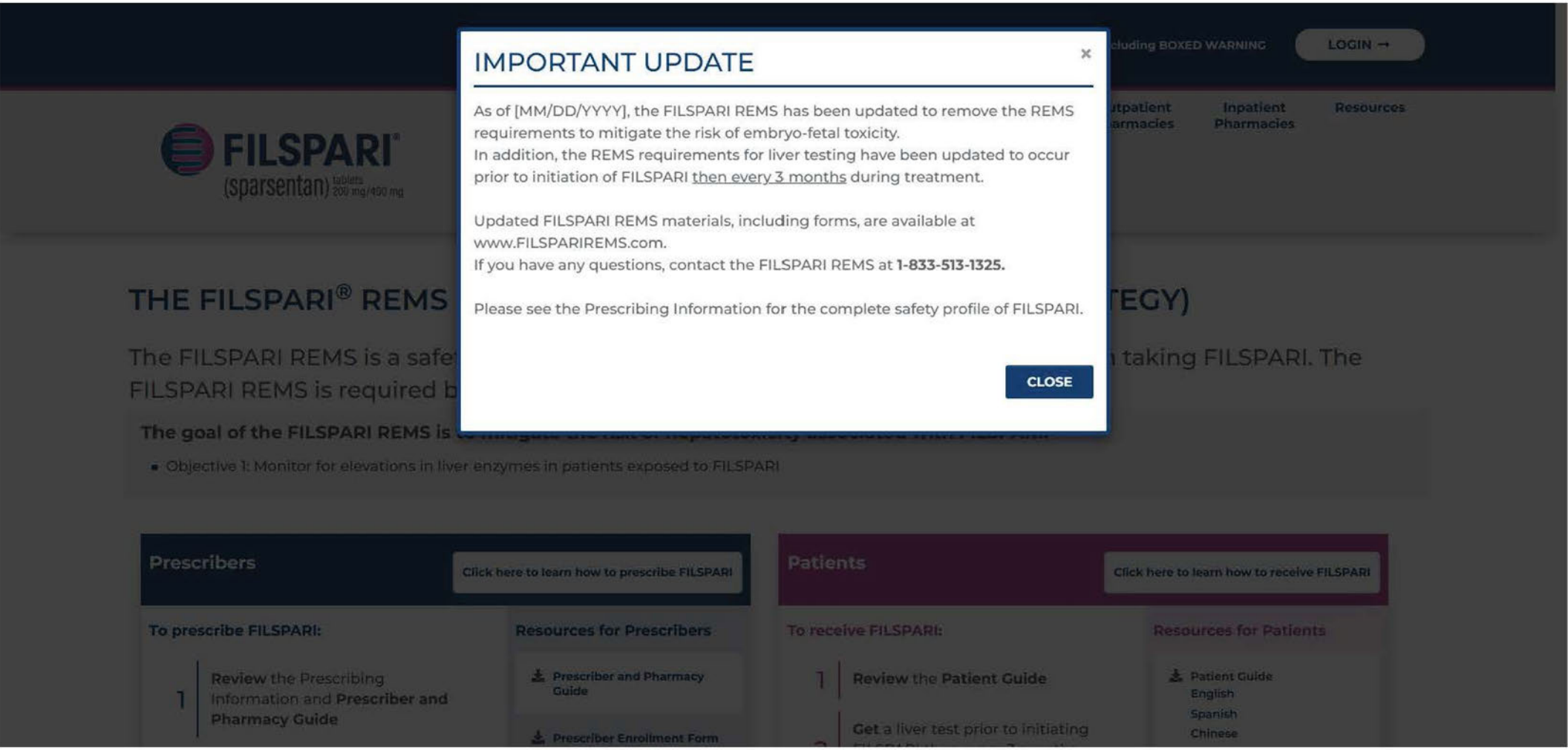
Below is a list of pharmacies certified in the FILSPARI REMS to dispense FILSPARI.

Download the list to spreadsheet format by clicking the Excel icon just above the column headers

Search/Filter the list by entering information in the text box below any column header

Sort the list by clicking on any column header

Name	City	State	ZIP	Phone Number	Fax Number
ABC Pharmacy	Philadelphia	PA	12345	555-555-1212	555-555-2323


IMPORTANT UPDATE
As of [MM/DD/YYYY], the FILSPARI REMS has been updated to remove the REMS requirements to mitigate the risk of embryo-fetal toxicity.
In addition, the REMS requirements for liver testing have been updated to occur prior to initiation of FILSPARI then every 3 months during treatment.
Updated FILSPARI REMS materials, including forms, are available at www.FILSPARIREMS.com.
If you have any questions, contact the FILSPARI REMS at 1-833-513-1325.
Please see the Prescribing Information for the complete safety profile of FILSPARI.
CLOSE
LOGIN
FILSPARI
(sparsentan)
Inpatient Pharmacies
Resources
THE FILSPARI® REMS
Prescribers
Click here to learn how to prescribe FILSPARI
Patients
Click here to learn how to receive FILSPARI
To prescribe FILSPARI:
Review the Prescribing Information and Prescriber and Pharmacy Guide
Resources for Prescribers
Prescriber and Pharmacy Guide
Prescriber Enrollment Form
To receive FILSPARI:
Review the Patient Guide
Resources for Patients
Patient Guide
English
Spanish
Chinese

THE FILSPARI® REMS (RISK EVALUATION AND MITIGATION STRATEGY)

The FILSPARI REMS is a safety program that manages the risk of liver problems when taking FILSPARI. The FILSPARI REMS is required by the Food and Drug Administration (FDA).

The goal of the FILSPARI REMS is to mitigate the risk of hepatotoxicity associated with FILSPARI:

- Objective 1: Monitor for elevations in liver enzymes in patients exposed to FILSPARI

Prescribers

Click here to learn how to prescribe FILSPARI

To prescribe FILSPARI:

1. **Review** the Prescribing Information and **Prescriber and Pharmacy Guide**
2. **Certify** by enrolling in the FILSPARI REMS by completing the **Prescriber Enrollment Form** and submitting it to the FILSPARI REMS
3. **Counsel** patients on the risk of hepatotoxicity associated with FILSPARI using the **Patient Guide**
4. **Assess** the patient's liver function
5. **Enroll** patients in the FILSPARI REMS by completing and submitting the **Patient Enrollment Form** to the FILSPARI REMS
6. **Monitor** patients based on REMS requirements

Resources for Prescribers

- Prescriber and Pharmacy Guide
- Prescriber Enrollment Form
- Patient Enrollment Form: English, Spanish, Chinese
- Patient Guide: English, Spanish, Chinese

Patients

Click here to learn how to receive FILSPARI

To receive FILSPARI:

1. **Review** the **Patient Guide**
2. **Get** a liver test prior to initiating FILSPARI then every 3 months during treatment
3. **Receive** counseling at treatment initiation and then every 3 months to understand the risk of liver problems associated with FILSPARI
4. **Enroll** in the FILSPARI REMS by completing the **Patient Enrollment Form** with your prescriber

Resources for Patients

- Patient Guide: English, Spanish, Chinese

Outpatient Pharmacies

Click here to learn how to dispense FILSPARI

To dispense FILSPARI:

1. **Designate** an authorized representative to carry out the certification process and oversee implementation and compliance with the FILSPARI REMS on behalf of the pharmacy
2. **Have** the authorized representative review the **Prescriber and Pharmacy Guide**
3. **Have** the authorized representative certify by enrolling in the FILSPARI REMS by completing the **Outpatient Pharmacy Enrollment Form**, and submitting it to the FILSPARI REMS
4. **Train** staff involved in dispensing FILSPARI and comply with REMS requirements
5. **Before dispensing**:
   - **Contact** the FILSPARI REMS online or by phone to verify the patient is enrolled in the FILSPARI REMS and the prescriber is certified
6. **Before dispensing; at initial dispense, then every 3 months:**
   - **Counsel** the patient on the risk of hepatotoxicity associated with FILSPARI
   - **Verify** and document the patient's liver testing is complete or the prescriber authorizes the refill
7. **Dispense** no more than a 90-days' supply
8. **Provide** dispensing data to the FILSPARI REMS

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide: English, Spanish, Chinese

Inpatient Pharmacies

Click here to learn how to dispense FILSPARI

To dispense FILSPARI:

1. **Designate** an authorized representative to carry out the certification process and oversee implementation and compliance with the FILSPARI REMS on behalf of the pharmacy
2. **Have** the authorized representative review the **Prescriber and Pharmacy Guide**
3. **Have** the authorized representative certify by enrolling in the FILSPARI REMS by completing the **Inpatient Pharmacy Enrollment Form**, and submitting it to the FILSPARI REMS
4. **Train** staff involved in dispensing FILSPARI and comply with REMS requirements
5. **Before dispensing**:
   - **Counsel** the patient on the risk of hepatotoxicity associated with FILSPARI
   - **Verify** and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete
6. **Dispense** no more than a 30-days' supply at discharge

Resources for Inpatient Pharmacies

- Prescriber and Pharmacy Guide
- Inpatient Pharmacy Enrollment Form
- Patient Guide: English, Spanish, Chinese

To learn more about the serious risk of hepatotoxicity associated with FILSPARI, please refer to the **US Prescribing Information including Boxed Warning**, the **Prescriber and Pharmacy Guide** and the **Patient Guide**.

Prescribers

Only prescribers certified by the FILSPARI REMS can prescribe FILSPARI and only pharmacies certified by the FILSPARI REMS can dispense FILSPARI to patients.

Patients must be enrolled in the FILSPARI REMS and follow all the safety rules in the FILSPARI REMS in order to receive FILSPARI.

Prescriber Requirements

How do I become certified in the FILSPARI REMS?

1. Review the following educational materials to understand the FILSPARI REMS and the risk of hepatotoxicity associated with FILSPARI:
   - **Prescribing Information**
   - **Prescriber and Pharmacy Guide**
2. Complete and submit the **Prescriber Enrollment Form:**
   - **Online**
   - **By fax**

How do I enroll my patient in the FILSPARI REMS and what steps should I take prior to treatment initiation?

1. Counsel the patient on the risk of hepatotoxicity associated with FILSPARI, the signs and symptoms of liver problems, to contact the prescriber if the patient has any signs or symptoms of liver problems, on the REMS requirements including the need to complete liver testing every 3 months during treatment, and that FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
2. Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
3. Provide the patient with the **Patient Guide**.
4. Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS:
   - **Online**
   - **By fax**

Once a patient is on FILSPARI, how often should I monitor my patient?

- Assess the patient's liver function every 3 months during treatment.
- Report any adverse events suggestive of hepatotoxicity to the REMS.

PDFs for Download

Resources for Prescribers

- **Prescriber and Pharmacy Guide**
- **Prescriber Enrollment Form**
- Patient Enrollment Form
  - English
  - Spanish
  - Chinese
- Patient Guide
  - English
  - Spanish
  - Chinese

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

CONTINUE

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

1234567890 CONTINUE

*First Name | Middle Initial | *Last Name

*Specialty (select one)
- ○ Nephrology
- ○ Other (please specify)

*Professional Designation (select one)
- ○ MD ○ DO ○ PA ○ NP

Office Practice/Clinic Name

*Address Line #1 | Address Line #2

*City | *State | *Zip

*State: -- Please Select --

Preferred Method of Contact (select one)
- ○ Fax ○ Email

*Email | *Office Phone | *Fax | Mobile Phone

Primary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

State: -- Please Select --

Email | Phone | Fax

Secondary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

State: -- Please Select --

Email | Phone | Fax

2 Prescriber Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

To become certified to prescribe, I must:

- Review the drug's Prescribing Information.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient on the:
  - Risk of hepatotoxicity associated with FILSPARI
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if the patient has any signs or symptoms of liver problems
  - REMS requirements including the need to complete liver testing every 3 months during treatment
  - FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
- Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
- Provide the patient with the **Patient Guide**.
- Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS.

During treatment, every 3 months, I must:

- Assess the patient's liver function.
- Counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the REMS.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI healthcare provider to comply with FILSPARI REMS requirements, and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Healthcare Provider Signature

CLEAR | CANCEL | SUBMIT

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

FILSPARI® REMS PRESCRIBER ENROLLMENT FORM

Instructions:

1. Review the Prescribing Information, and the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Prescriber Enrollment Form** to the REMS.

* *Indicates required field*

1 Prescriber Information

*National Provider Identifier (NPI) #

1234567890 CONTINUE

*First Name | Middle Initial | *Last Name

*Specialty (select one)
- ○ Nephrology
- ◉ Other (please specify)

*Professional Designation (select one)
- ○ MD ○ DO ○ PA ○ NP

*Other Specialty

Other

Office Practice/Clinic Name

*Address Line #1 | Address Line #2

*City | *State | *Zip

-- Please Select --

Preferred Method of Contact (select one)
- ○ Fax ○ Email

*Email | *Office Phone | *Fax | Mobile Phone

Primary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

-- Please Select --

Email | Phone | Fax

Secondary Office Contact Information

First Name | Last Name

Address Line #1 | Address Line #2

City | State | Zip

-- Please Select --

Email | Phone | Fax

2 Prescriber Agreement

By completing, signing, and submitting this form, I agree and acknowledge that:

To become certified to prescribe, I must:

- Review the drug's Prescribing Information.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing the **Prescriber Enrollment Form** and submitting it to the REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient on the:
  - Risk of hepatotoxicity associated with FILSPARI
  - Signs and symptoms of liver problems
  - Need to contact the prescriber if the patient has any signs or symptoms of liver problems
  - REMS requirements including the need to complete liver testing every 3 months during treatment
  - FILSPARI is only available through a restricted distribution program using the **Patient Guide**.
- Assess the patient's liver function. Document and submit to the REMS using the **Patient Enrollment Form**.
- Provide the patient with the **Patient Guide**.
- Enroll the patient by completing the **Patient Enrollment Form** and submitting it to the REMS.

During treatment, every 3 months, I must:

- Assess the patient's liver function.
- Counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the REMS.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI healthcare provider to comply with FILSPARI REMS requirements, and I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Healthcare Provider Signature

CLEAR | CANCEL | SUBMIT

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Prescriber Enrollment Submitted Successfully

Thank you for submitting your information to enroll in the FILSPARI REMS.

A confirmation of this submission has been sent to the email address provided. This email will also include instructions on how to create your web account for the FILSPARI REMS.

If you do not receive the email within the next few hours or would like to update your enrollment information at any time, please contact the FILSPARI REMS for assistance at 1-833-513-1325.

Patients

What is FILSPARI?

FILSPARI is a prescription medicine used to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

What is the serious risk of FILSPARI?

FILSPARI can cause liver problems. Patients must have their liver function checked before starting FILSPARI then every 3 months during treatment with FILSPARI.

How do I become enrolled in the FILSPARI REMS?

1. **Read** the **Patient Guide**.
2. **Review** and discuss the benefits and risks associated with FILSPARI with your prescriber.
3. **Enroll** in the FILSPARI REMS by completing the **Patient Enrollment Form** with your prescriber.

Please refer to the details provided below and in the **Patient Guide** for REMS requirements.

What are the FILSPARI REMS requirements for me?

To receive FILSPARI, you must:

- Talk to your prescriber to ensure the benefits outweigh the risks of FILSPARI.
- Receive counseling from your prescriber on the risk of liver problems using the **Patient Guide**.
- Enroll in the FILSPARI REMS by completing and signing the **Patient Enrollment Form**.
- Get a liver test before starting FILSPARI then every 3 months during treatment.
- **Be sure you get your liver test every 3 months during treatment. Your certified pharmacy will call you every 3 months to provide counseling and confirm completion of a liver test before shipping your refill. If you do not get your liver test, you may not receive your FILSPARI on time.**

How will I receive my FILSPARI?

Only pharmacies that are certified in the FILSPARI REMS can provide FILSPARI to you. In some cases, your insurance company may require you to use a specific certified pharmacy.

Your certified pharmacy ships your FILSPARI refill to you. The certified pharmacy will confirm that you have completed a liver test (every 3 months during treatment) before refilling your prescription. **It is important that your certified pharmacy is able to contact you in order to avoid delays in your refills**.

If you have questions or concerns about FILSPARI, talk to your prescriber. Please visit **www.FILSPARIREMS.com** or call **1-833-513-1325** for more information about the FILSPARI REMS.

PDFs for Download

Resources for Patients

Patient Guide
English
Spanish
Chinese

Outpatient Pharmacies

Only a limited number of certified pharmacies will dispense FILSPARI for outpatients. All outpatient pharmacies that wish to stock FILSPARI must contract with Travere Therapeutics, Inc., and must have the authorized representative certify by enrolling in the FILSPARI REMS.

Contact the FILSPARI REMS to obtain contact information for certified outpatient pharmacies and distributors who are authorized to ship to certified outpatient pharmacies.

To become certified to dispense FILSPARI, outpatient pharmacies must:

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
2. Have the authorized representative review the **Prescriber and Pharmacy Guide**.
3. Have the authorized representative certify by enrolling in the REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the REMS:
   - **By fax**
4. Train all relevant staff involved in dispensing on REMS requirements using the **Prescriber and Pharmacy Guide**.
5. Establish processes and procedures to verify the patient is enrolled and the prescriber is certified.
6. Establish processes and procedures to document and submit confirmation of counseling on the risk of hepatotoxicity.
7. Establish processes and procedures to verify and document the patient's liver testing is complete or the prescriber authorizes the refill.

To ensure compliance with FILSPARI REMS requirements, outpatient pharmacies must:

1. Before dispensing FILSPARI, the outpatient pharmacy must:
   - **Verify** the patient is enrolled and the prescriber is certified through the processes and procedures established as a requirement of the REMS.
2. Before dispensing FILSPARI; at initial dispense, then every 3 months, the outpatient pharmacy must:
   - **Counsel** the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
     - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing.
   - **Verify** and document the patient's liver testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS.
3. At all times, the outpatient pharmacy must:
   - **Dispense** no more than a 90-days' supply.
     - A certified prescriber may be eligible to provide the outpatient pharmacy a one-time authorization to dispense a greater than 90-days' supply. The outpatient pharmacy must report the reason to the FILSPARI REMS. For information on the eligibility to dispense more than a 90-days' supply and related authorization process, contact the FILSPARI REMS at 1-833-513-1325.
   - **Report** adverse events suggestive of hepatotoxicity to the REMS.
   - **Not** distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
   - **Maintain** and submit records of product dispensing data to the REMS.
   - **Maintain** records that all processes and procedures are in place and are being followed.
   - **Comply** with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and being followed.
4. To maintain certification to dispense, the outpatient pharmacy must:
   - **Have a new authorized representative enroll by completing and submitting** an **Outpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Contact the FILSPARI REMS at 1-833-513-1325 for more information on becoming a certified outpatient pharmacy.

Login is available for certified pharmacies.

PDFs for Download

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Inpatient Pharmacies

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the FILSPARI REMS may stock FILSPARI for patients being treated in the inpatient setting.

Contact the FILSPARI REMS to obtain contact information for certified inpatient pharmacies and distributors who are authorized to ship to certified inpatient pharmacies.

To become certified to dispense FILSPARI, inpatient pharmacies must:

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
2. Have the authorized representative review the **Prescriber and Pharmacy Guide**.
3. Have the authorized representative certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS:
   - **Online**
   - **By fax**
4. Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
5. Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

To ensure compliance with FILSPARI REMS requirements, inpatient pharmacies must:

1. Before dispensing FILSPARI, the inpatient pharmacy must:
   - **Counsel** the patient on the risk of hepatoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
     - Counsel the patient on the risk of hepatotoxicity, the signs and symptoms of liver problems, the need to contact the prescriber if they have any signs or symptoms of liver problems, and the need to complete liver testing.
   - **Verify** and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete by contacting the FILSPARI REMS **online** or by phone at 1-833-513-1325.
     - Liver testing will be required every 3 months during treatment.
2. At discharge, the inpatient pharmacy must:
   - **Dispense** no more than a 30-days' supply.
3. At all times, the inpatient pharmacy must:
   - **Report** adverse events suggestive of hepatotoxicity to the REMS.
   - **Not** distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
   - **Maintain** records that all processes and procedures are in place and are being followed.
   - **Comply** with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and being followed.
4. To maintain certification to dispense, the inpatient pharmacy must:
   - **Have a new authorized representative enroll by completing and submitting** an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Login is available for certified pharmacies.

PDFs for Download

Resources for Inpatient Pharmacies

Prescriber and Pharmacy Guide

Inpatient Pharmacy Enrollment Form

Patient Guide
English
Spanish
Chinese

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

CONTINUE

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

1234567890

*Inpatient Pharmacy Name

*Inpatient Pharmacy Location

○ Hospital ○ Nursing Home ○ Hospice ○ Mental Health Facility
○ Assisted Living ○ Prison ○ Rehabilitation Facility ○ Other (please specify)

Drug Enforcement Administration Number (DEA #)

Inpatient Pharmacy Address

*Address Line #1 | Address Line #2

*City | *State (-- Please Select --) | *Zip

*Phone | *Fax

Pharmacy Ship To Contact

*First Name | *Last Name

Pharmacy Shipping Address

☐ Pharmacy Shipping Address - Same as above

*Address Line #1 | Address Line #2

*City | *State (-- Please Select --) | *Zip

*Phone | *Fax

2 Inpatient Pharmacy Authorized Representative Information

*First Name | *Last Name

Position/Title:

○ Hospital pharmacist ○ Head of Pharmacy and Therapeutics (P&T) committee
○ Other (please specify)

*Authorized Representative Office Phone | *Fax | *Authorized Representative Email

*Contact Preference (select one):

○ Email ○ Fax

3 Inpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

- Carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

Before dispensing FILSPARI, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

At discharge, my pharmacy must:

- Dispense no more than a 30-days' supply.

At all times, my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI inpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Authorized Representative Signature

CLEAR | CANCEL | SUBMIT

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

FILSPARI® REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions:

1. Review the **Prescriber and Pharmacy Guide**.
2. Enroll by completing all fields below and submitting this **Inpatient Pharmacy Enrollment Form** to the REMS.

Due to the risk of hepatotoxicity, FILSPARI is available only through a restricted program called the FILSPARI REMS (Risk Evaluation and Mitigation Strategy). All inpatient pharmacies that wish to stock FILSPARI must certify by enrolling in the FILSPARI REMS.

* *Indicates required field*

1 Inpatient Pharmacy Information

*Facility National Provider Identifier (NPI) #

1234567890

*Inpatient Pharmacy Name

*Inpatient Pharmacy Location

○ Hospital ○ Nursing Home ○ Hospice ○ Mental Health Facility
○ Assisted Living ○ Prison ○ Rehabilitation Facility ◉ Other (please specify)

Drug Enforcement Administration Number (DEA #)

*Other Inpatient Pharmacy Location

Other

Inpatient Pharmacy Address

*Address Line #1

Address Line #2

*City

*State

-- Please Select --

*Zip

*Phone

*Fax

Pharmacy Ship To Contact

*First Name

*Last Name

Pharmacy Shipping Address

☑ Pharmacy Shipping Address - Same as above

2 Inpatient Pharmacy Authorized Representative Information

*First Name

*Last Name

Position/Title:

○ Hospital pharmacist ○ Head of Pharmacy and Therapeutics (P&T) committee
◉ Other (please specify)

*Other Position/Title

Please Specify

*Authorized Representative Office Phone

*Fax

*Authorized Representative Email

*Contact Preference (select one):

○ Email ○ Fax

3 Inpatient Pharmacy Authorized Representative Agreement

As the pharmacy authorized representative, to become certified to dispense FILSPARI, I must:

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- Review the **Prescriber and Pharmacy Guide**.
- Certify by enrolling in the REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the REMS.
- Train all relevant staff involved in dispensing on the REMS requirements using the **Prescriber and Pharmacy Guide**.
- Establish processes and procedures to verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

Before dispensing FILSPARI, my pharmacy must:

- Counsel the patient on the risk of hepatotoxicity. Document and submit confirmation of counseling through the processes and procedures established as a requirement of the REMS.
- Verify and document the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, and liver testing is complete.

At discharge, my pharmacy must:

- Dispense no more than a 30-days' supply.

At all times, my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the REMS.
- Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by Travere Therapeutics, Inc. or a third party acting on behalf of Travere Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, my pharmacy must:

- Have a new authorized representative enroll by completing and submitting an **Inpatient Pharmacy Enrollment Form**, if the authorized representative changes.

Provide Signature Below

By signing below, I acknowledge the above agreements and my obligations as a FILSPARI inpatient pharmacy authorized representative and agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy. I understand my personally identifiable information provided above will be shared with Travere Therapeutics, Inc., its agents or contractors and entered into a database for the FILSPARI REMS. I agree that I may be contacted in the future by mail, email, fax, and/or phone concerning FILSPARI, the FILSPARI REMS, and other FILSPARI programs and services.

☐ *Authorized Representative Signature

CLEAR | CANCEL | SUBMIT

Healthcare providers should report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325. Report all other suspected adverse events or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

If you have any questions, require additional information, or need further copies of FILSPARI REMS materials, please visit the **REMS Website** at www.FILSPARIREMS.com, or call the FILSPARI REMS at 1-833-513-1325.

Inpatient Pharmacy Enrollment Submitted Successfully

Thank you for submitting your information to enroll in the FILSPARI REMS.

A confirmation of this submission has been sent to the email address provided. This email will also include instructions on how to create your web account for the FILSPARI REMS.

If you do not receive the email within the next few hours or would like to update your enrollment information at any time, please contact the FILSPARI REMS for assistance at 1-833-513-1325.

Resources

Resources for Prescribers

- Prescriber and Pharmacy Guide
- Prescriber Enrollment Form
- Patient Enrollment Form
  - English
  - Spanish
  - Chinese
- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Patients

- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Outpatient Pharmacies

- Prescriber and Pharmacy Guide
- Outpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Resources for Inpatient Pharmacies

- Prescriber and Pharmacy Guide
- Inpatient Pharmacy Enrollment Form
- Patient Guide
  - English
  - Spanish
  - Chinese

Contact Us

Phone

1-833-513-1325

Fax

1-833-483-4736

Hours of Operation

Monday - Friday
8:00 AM - 8:00 PM
EST

Report adverse events suggestive of hepatotoxicity to the FILSPARI REMS at 1-833-513-1325.

Report all other suspected adverse events, or product quality complaints associated with FILSPARI to Travere Therapeutics, Inc. at 1-877-659-5518 or FDA at 1-800-FDA-1088 or online at **www.fda.gov/medwatch**.

For FILSPARI REMS information contact:
Phone: 1-833-513-1325
Fax: 1-833-483-4736

Certified Outpatient Pharmacies

Below is a list of pharmacies certified in the FILSPARI REMS to dispense FILSPARI.

Download the list to spreadsheet format by clicking the Excel icon just above the column headers

Search/Filter the list by entering information in the text box below any column header

Sort the list by clicking on any column header

Name	City	State	ZIP	Phone Number	Fax Number
ABC Pharmacy	Philadelphia	PA	12345	555-555-1212	555-555-2323

This is a r r s a i f a A l c r ic r c rd ha was sig d l c r ically. F ll wi g his ar ma if s a i s f a y a d all l c r ic sig a ur s f r his l c r ic r c rd.

/s/ A

SELEN D DECONTI
08/27/2025 01:15:40 PM A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

CLINICAL REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs

Clinical Summary

NDA/Supplement #:	216403/Supp-005
Date of submission:	October 28, 2024
Review date:	August 25, 2025
Applicant:	Travere Therapeutics
Product:	Filspari (sparsentan)
Subject:	Liver Monitoring Frequency and REMS Modification Embryo-fetal Toxicity and REMS Elimination

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1 Introduction

Sparsentan (FILSPARI) is a dual endothelin receptor antagonist (ERA) and angiotensin receptor blocker (ARB) initially granted accelerated approval on February 17, 2023, for reducing proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally defined as a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g. The accelerated approval was based on interim results from the ongoing Phase 3 PROTECT Study, which demonstrated proteinuria reduction compared to the active control, irbesartan.

On March 5, 2024, the Applicant submitted an efficacy supplement containing completed PROTECT Study results to fulfill their postmarketing requirement and support traditional approval. Sparsentan received full approval on September 5, 2024, with an updated indication to slow kidney function decline in adults with primary IgAN at risk for disease progression.

On October 28, 2024, Travere Therapeutics, the Applicant, submitted a supplemental application and amendment on May 19, 2025, proposing two significant changes:

1. Modification of the liver testing frequency in the product labeling (from monthly for 12 months, then every 3 months during treatment to every 3 months during treatment).
2. Removal of the risk of embryo-fetal toxicity (EFT) from the Risk Evaluation and Mitigation Strategy (REMS).

On November 20, 2024, DCN consulted the Division of Hepatology and Nutrition (DHN) to review the supplement and opine on the Applicant's proposal for decreased frequency of liver monitoring. DHN requested additional data from the Applicant regarding sparsentan liver-related events; refer to the Information Response, dated March 17, 2025.

2 Background

2.1 ERA Class Hepatotoxicity Risk Profile

Hepatotoxicity is a class risk for all six approved endothelin receptor antagonists (ERAs): bosentan, ambrisentan, macitentan, sparsentan, aprocitentan, and atrasentan. However, the severity of this risk varies significantly across the class, resulting in different regulatory approaches.

Bosentan presents the highest hepatotoxicity risk, with rare cases of hepatic cirrhosis after prolonged use and postmarketing reports of liver failure. Consequently, bosentan was the first ERA approved with a REMS for hepatotoxicity and requires a boxed warning with monthly aminotransferase (AT) and bilirubin monitoring throughout treatment.

Four ERAs (macitentan, ambrisentan, atrasentan, and aprocitentan) have labeling warnings for hepatotoxicity requiring baseline liver enzyme testing and monitoring "as clinically indicated" during treatment. Their clinical data at this time does not warrant a REMS.

Clinical development data revealed that sparsentan's hepatotoxicity risk requires a monitoring strategy that falls between the intensive surveillance required for high-risk bosentan and the less frequent monitoring used for the four lower-risk ERAs. During NDA review, DHN identified: 1) An imbalance in AT elevations within Temple's Corollary 2) Probable DILI cases with positive rechallenge and 3) Extended time to DILI onset (months rather than weeks).[1]

Given sparsentan's hepatotoxicity risk, approval included a REMS to ensure the monitoring occurred prior to dispensing the drug, with baseline liver enzyme testing followed by monthly monitoring for 12 months, then quarterly thereafter. Additionally, given limited exposure data (only 500 subjects in the integrated safety summary—insufficient for detecting Hy's Law cases), the Applicant was given a post-marketing requirement (PMR-4330-5) to conduct a single-arm safety study to further characterize DILI risk.[2]

[1] See the Hayshi, P. DHN Consult Review dated September 20, 2022, original NDA Integrated Review dated February 17, 2023, Hayshi, P. DHN Consult Review for sNDA dated August 19, 2024, sNDA Integrated Review supporting final approval dated September 5, 2024

[2] See the Southworth, M. REMS Memo dated February 16, 2023

2.2 ERA Class Embryo-fetal toxicity Risk Profile

Embryo-fetal toxicity is a class risk for all ERAs based on animal studies. At the time of sparsentan's approval, all ERA products required a REMS to prevent fetal exposure. Since sparsentan's EFT profile is consistent with the ERA class, a REMS was required at approval.[3]

2.3 Labeling

Labeling describes each risk, monitoring requirements, and outlines the REMS requirements for hepatotoxicity and embryo-fetal toxicity. Appendix A provides a summary of the relevant labeling.

2.4 REMS

The REMS requires elements to assure safe use (ETASU) including healthcare provider certification, patient enrollment, pharmacy certification, and documentation of liver enzyme testing and pregnancy testing. The REMS mitigates hepatotoxicity risk by ensuring recommended liver testing occurs and mitigates EFT risk by confirming patients are not pregnant at initiation and minimizing fetal exposure during treatment. All required testing (liver and pregnancy) must be completed before drug dispensing at initiation and throughout treatment.

Importantly, the REMS ensures these safety processes occur before dispensing sparsentan but does not assess the underlying risk profiles of hepatotoxicity or EFT.

3 Data Analysis

3.1 DHN Key Findings for the Risk of Hepatotoxicity

The Applicant submitted reports of hepatotoxicity with sparsentan use from clinical trials (PROTECT, DUPLEX, and DUET) prior to approval, and those reported from open-label extension (OLE) phases and REMS since approval. The clinical trial cases were previously analyzed by DHN during NDA review and provided the basis for current labeling and REMS requirements (refer to DHN review and the original NDA reviews for details). [4] Exposure data is provided in Appendix E. DHN was consulted to review the data and provided an overview of key findings, focusing primarily on cases reported post-approval, during the Mid-Cycle Meeting on April 3, 2025 (Appendix G).

3.1.1 Post-Approval Hepatotoxicity Events

Since approval through August 1, 2024, twenty-seven (27) patients experienced transaminase elevations >3× ULN and/or serious liver-related events. These occurred in 20 patients during OLE phases of the clinical trials (PROTECT n=6; DUPLEX n=10; DUET n=4) and 7 patients in the REMS population.

3.1.2 Severity Assessment

Among 15 cases with transaminase elevations >5× ULN identified post-approval, DHN assessed:

[3] See the Southworth, M. REMS Memo dated February 16, 2023

[4] See the Hayshi, P. DHN Consult Review dated September 20, 2022, original NDA Integrated Review dated February 17, 2023, Hayshi, P. DHN Consult Review for sNDA dated August 19, 2024, sNDA Integrated Review supporting final approval dated September 5, 2024

- Four cases as probable DILI
- Ten cases as possible/unlikely DILI
- One case as indeterminate for DILI

3.1.3 Hy's Law Analysis

Review of updated eDISH plots (Appendix B) indicates that while some patients exhibited ALT and AST elevations >10× ULN, including one case with AST approximately 50× ULN associated with COVID pneumonia, no cases met Hy's Law criteria. This finding is consistent with pre-approval safety data.

3.1.4 Data Collection Limitations

DHN expressed concern about potential under-reporting or incomplete data capture, evidenced by only 6 patients represented in post-market eDISH plots (Appendix B) despite approximately 2,000 exposed patients in the REMS. For REMS participants, liver test data is only available for those with reported abnormal values, limiting assessment of the overall distribution of liver enzyme values across the full patient population. One post-market case (Case (b) (6), detailed in Appendix C) demonstrated infrequent liver testing documentation in REMS data despite patient attestation to monthly testing compliance. When questioned, the Sponsor could not provide explanation and opened an investigation to query the prescriber for additional details.

3.1.5 Conclusion and Recommendation

Despite data collection limitations, DHN supports the Applicant's proposed monitoring schedule of every 12 weeks (3 months) from sparsentan initiation throughout treatment, based on: 1) Absence of Hy's Law cases with additional exposure 2) Consistency with PROTECT study monitoring that successfully detected hepatotoxicity and 3) Maintained REMS safeguards for pre-dispensing verification.

DHN recommends that labeling and REMS be updated to reflect the proposed quarterly monitoring schedule while preserving detailed prescriber guidance for managing transaminase elevations and clinical symptoms.

3.2 Key Findings for the Risk of Embryo-fetal Toxicity

The prior reviews detailing postmarketing EFT findings in humans and recommendation for the REMS modification are provided in 3 reviews conducted by DPMH, DCN, and DRM, filed in DARRTS. The Agency determined that postmarketing data supports removal of the EFT risk from the REMS for all ERAs, and that labeling is sufficient to mitigate the risk. [5]

[5] See DeConti, S. Clinical Review dated February 28, 2025, and REMS Modification Notification dated March 11, 2025.

4 Discussion

The Applicant submitted this efficacy supplement proposing two REMS modifications: reducing liver monitoring frequency from monthly for 12 months then quarterly to quarterly throughout treatment and removing embryo-fetal toxicity (EFT) from the REMS.

Hepatotoxicity Monitoring

Post-approval safety data demonstrates continued hepatotoxicity risk consistent with pre-approval findings. Since approval, 27 patients have experienced transaminase elevations >3× ULN and/or serious liver-related events across clinical trials OLE (n=20) and REMS (n=7). Among 15 cases with elevations >5× ULN, DHN assessed four as probable DILI and ten as possible/unlikely DILI. Importantly, no cases met Hy's Law criteria, consistent with pre-approval data.

The Applicant's proposed quarterly monitoring aligns with the PROTECT study schedule and is supported by accumulated safety experience from the clinical trials. While hepatotoxicity rates appear higher in quarterly monitoring periods (PROTECT: 3.5%; open-label extension: 3.2%) compared to monthly monitoring captured in REMS data (0.3%), these numerical differences cannot be interpreted as evidence favoring an improved risk profile due to fundamental limitations in REMS data collection. The REMS relies on attestation that monitoring occurred rather than capturing comprehensive clinical data; while hepatotoxicity cases of interest are requested through the REMS, the passive collection method results in frequently incomplete data sets. Thus, the risk of severe DILI in larger post-market populations remains incompletely characterized and clinical data collected through the PMR will likely provide more robust characterization of the hepatotoxicity risk.

The Applicant conducted a survey of nephrologists to assess patient impact associated with the monthly testing requirement (Appendix F). Since the Agency did not review the survey methodology prior to implementation, the validity of the results cannot be assured. Nevertheless, the survey provides anecdotal evidence regarding the healthcare burden imposed by the monthly testing requirement.

Several factors support the proposed monitoring reduction: 1) No Hy's Law cases identified despite additional exposure 2) Quarterly monitoring used to detected hepatotoxicity in clinical trials 3) Reduced healthcare system burden while maintaining REMS safeguards 4) Continued prescriber education and patient counseling within the labeling and REMS.

As of April 30, 2025, the ongoing PMR study (PMR-4330-5) has enrolled only 147 of 3,000 expected patients, with final results not due until April 2028. Given this limited post-market exposure data, we will require interim safety analyses in Periodic Safety Reports (PSRs) following the quarterly monitoring implementation and interim analysis of the PMR when enrollment reaches 500 and 1500 patients. If severe cases emerge, reverting to monthly monitoring may be necessary.

Embryo-Fetal Toxicity

In a prior action (March 2025), the Agency determined that labeling is sufficient to mitigate EFT risk across the ERA class. Sparsentan's labeling aligns with the class changes and includes appropriate risk mitigation measures: pregnancy contraindication, boxed warning, pre-treatment pregnancy testing requirements, and effective contraception recommendations. These labeling elements adequately address the EFT risk without requiring REMS. We will require enhanced pharmacovigilance with inclusion

of a summary analysis of reports of pregnancy and embryo-fetal and neonatal toxicity as part of the required PSRs.

5 Conclusion

The accumulated safety data supports quarterly liver monitoring within the REMS framework while maintaining adequate safety through continued prescriber certification, patient enrollment, and pre-dispensing laboratory verification. The EFT REMS removal aligns with the class-wide Agency determination. Both proposed modifications are acceptable with enhanced post-market surveillance to monitor the impact of reduced hepatotoxicity monitoring frequency and future reports of pregnancy and embryo-fetal toxicity as part of the required PSRs.

6 Recommendation

The review team finds the proposed labeling changes and corresponding REMS modification acceptable. The efficacy supplement is approvable. Enhanced post-marketing surveillance will be implemented to monitor the risks of hepatotoxicity and EFT following these changes. For the hepatotoxicity risk, interim safety analyses will be included in PSRs and an interim analysis of the PMR should be submitted when enrollment reaches 500 and 1500 patients. For the EFT risk, enhanced pharmacovigilance will include a summary analysis of reports of pregnancy and embryo-fetal toxicity as part of the required PSRs.

7 Appendices

Appendix A. Approved Labeling, Revised September 2024

Hepatotoxicity

The approved labeling for FILSPARI includes a boxed Warning and recommended monitoring for hepatotoxicity and dosage adjustment and Warning for hepatotoxicity and FILSPARI REMS. Liver monitoring involves an initial testing of aminotransferase levels and total bilirubin prior to starting FILSPARI and monthly testing for the first 12 months of treatment, followed by testing every 3 months thereafter. Dosage adjustment for AT elevations is described in-depth in the labeling and prescribers are instructed to interrupt treatment, and monitor aminotransferase levels and bilirubin at least weekly, and INR as needed, until the levels return to pretreatment values and the patient is asymptomatic. Treatment is not to resume in patients who have experienced clinical symptoms of hepatotoxicity or in patients whose hepatic enzyme levels and bilirubin have not returned to pretreatment levels. The requirements under the REMS are designed to ensure initial and ongoing assessment of liver function and patient adherence to the prescribed monitoring schedule.

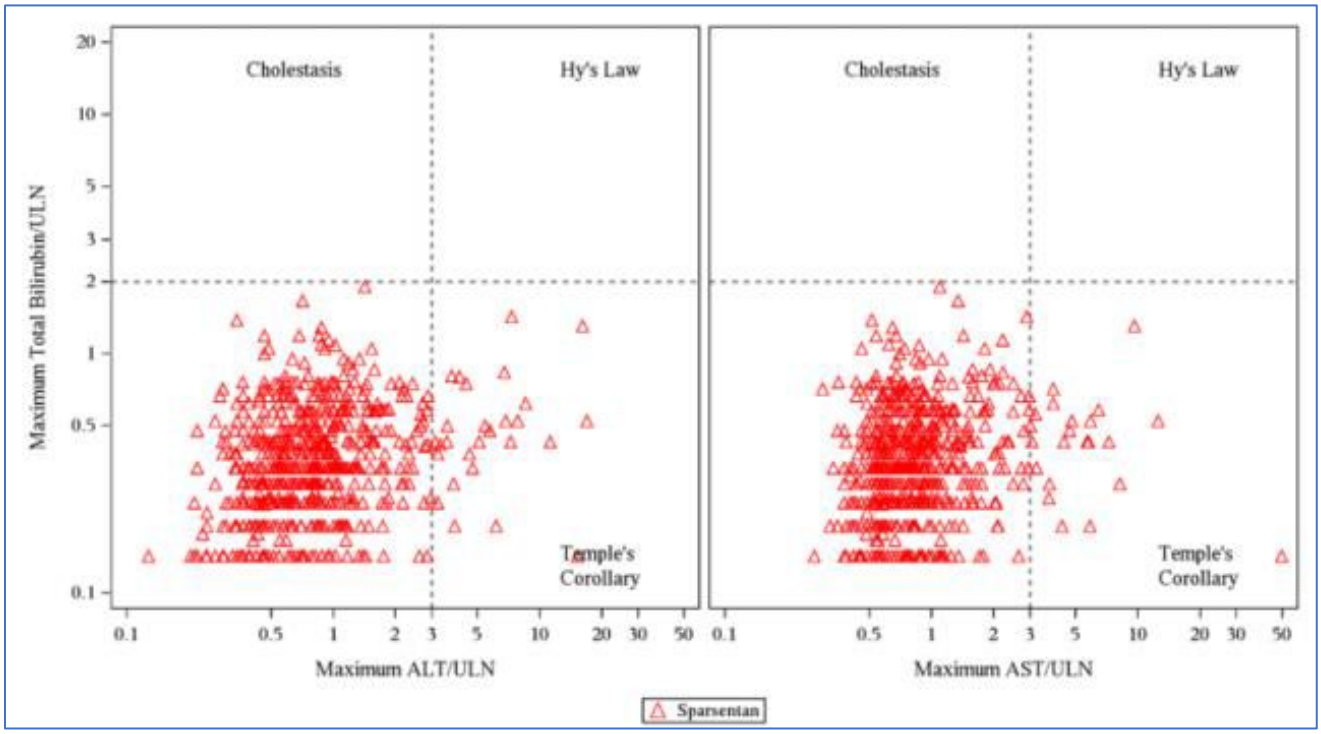
Embryofetal Toxicity

The approved labeling for FILSPARI includes a contraindication for use during pregnancy, boxed Warning, required monitoring for pregnancy in patients who can become pregnant, Warning for EFT, Filspari REMS Warning, pregnancy information and animal data for Use in Specific Populations, and Patient Counseling information. Pregnancy testing involves an initial test prior to starting FILSPARI and monthly testing during treatment up to 1 month following discontinuation. The requirements under the REMS are designed to ensure initial and ongoing pregnancy testing and patient adherence to the prescribed monitoring schedule.

Appendix B. eDISH Plots and Analysis

DHN requested the Applicant submit updated eDISH plots including local/outside laboratory results for the All Sparsentan group of the rare glomerular disease (RGD) study pool only, including the OLE phases (Figure 1). The updated eDISH plots do not identify any cases meeting Hy's Law criteria. Some data points have shifted within the Temple's Corollary quadrant, including a case from the DUPLEX study (Subject (b) (6), which showed an AST level of approximately 50× upper limit of normal (ULN). This case occurred 2 weeks after treatment discontinuation and was associated with COVID pneumonia. Overall, all points within the revised plot still lie within the Temple's Corollary quadrant.

Figure 1. eDISH Scatter Plots of Maximum Total Bilirubin/ULN vs Maximum ALT/ULN and Maximum AST/ULN, All Sparsentan group of the rare glomerular disease (RGD) study pool



Source: S-005 Information Request Response, dated March 3, 2025

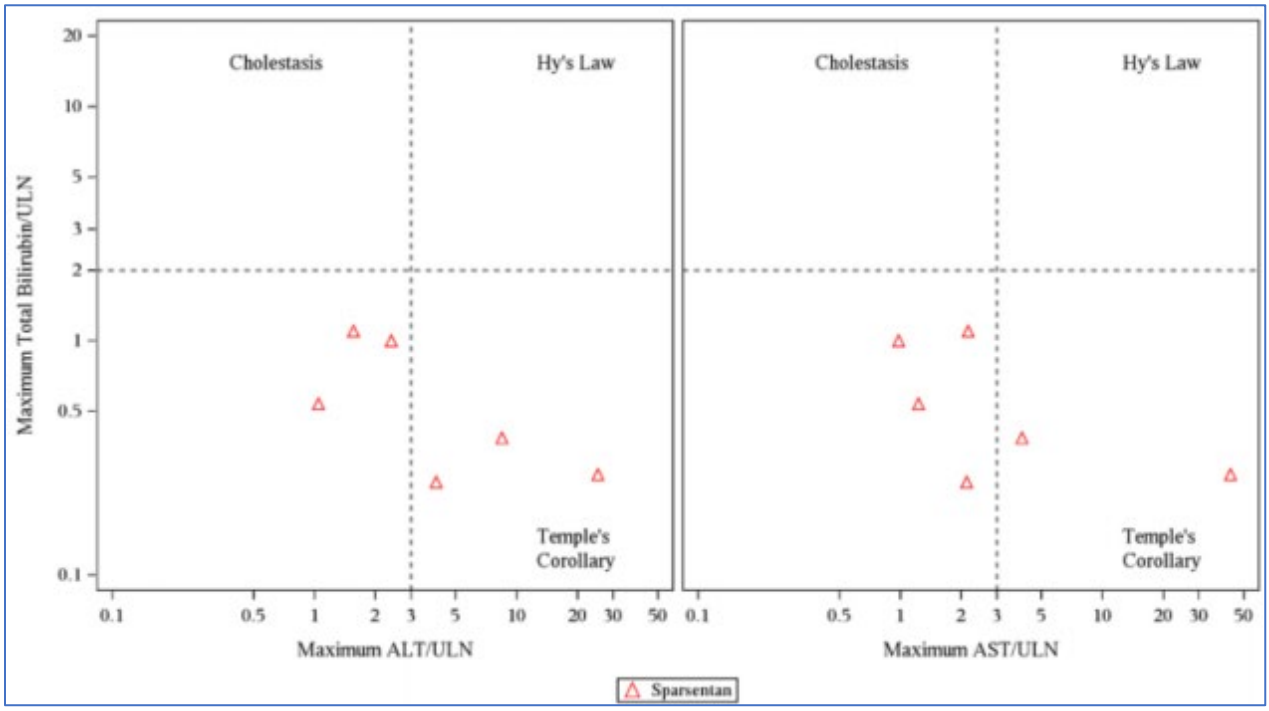
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RGD = rare glomerular disease ULN = upper limit of normal

Notes: Data cutoff dates were 01AUG2024 for PROTECT, DUPLEX. Data for DUET is based on the database lock date of 08 May 2024.

All Sparsentan Group in RGD study pool includes patients who received at least 1 dose of sparsentan during any treatment period. It includes patients who received 200 mg sparsentan in DUET and patients who received irbesartan during the double-blind period and continued to receive sparsentan during the open-label extension.

The eDISH plots for postmarketing cases only include data from 6 patients who had abnormalities reported (Figure 2) in the REMS, which limits the ability to assess the overall distribution of liver enzyme values across the full patient population. Review of the eDISH plots indicates that while some patients exhibited ALT and AST elevations >5× ULN, no cases met Hy's Law criteria.

Figure 2. eDISH Scatter Plots of Maximum Total Bilirubin/ULN vs Maximum ALT/ULN and Maximum AST/ULN, REMS Participants with Abnormal Values

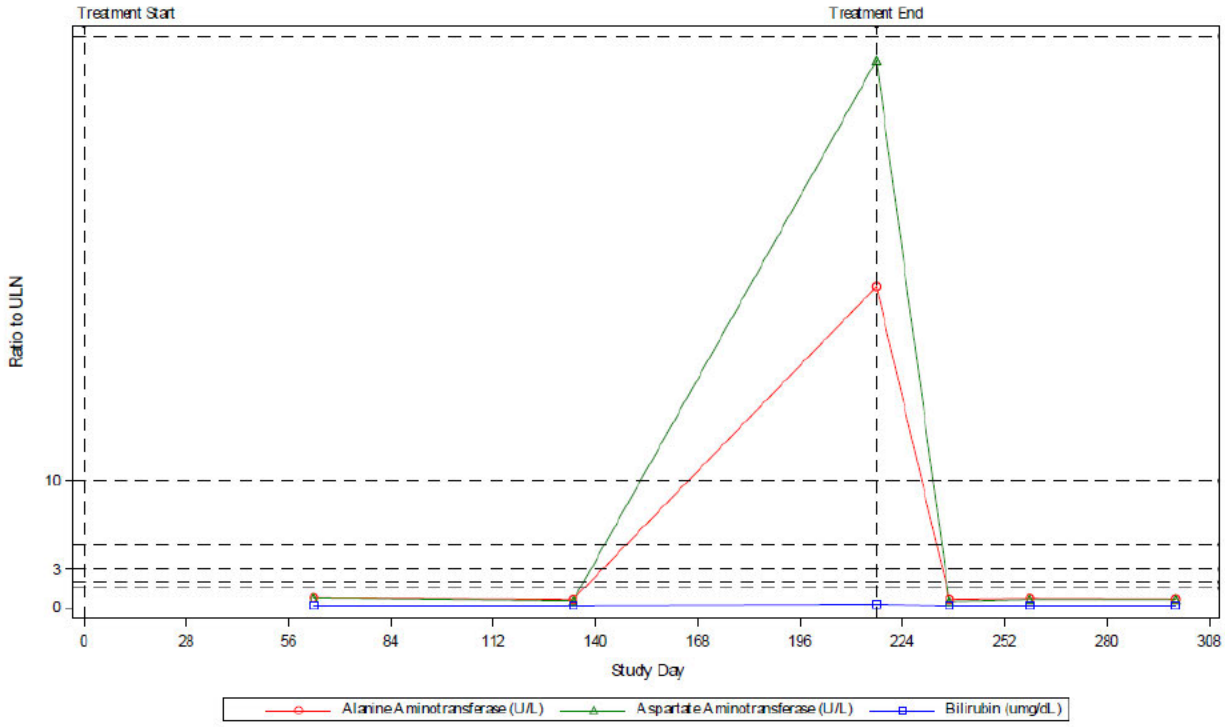


Source: S-005 Information Request Response, dated March 3, 2025
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RGD = rare glomerular disease ULN = upper limit of normal
Note: Data are based on a data cutoff date of 01 August 2024. Plot includes central and local laboratory results.

Appendix C: Case [redacted] (b) (6) (REMS Participant)

The case involves a 31-40-year-old female patient with IgAN who experienced serious hepatic enzyme elevation 217 days after initiating treatment with sparsentan 400 mg daily. Sparsentan was permanently discontinued on the same day. When tested again 3 weeks after discontinuation, the hepatic enzymes were normal and remained normal when tested 6 weeks after discontinuation of sparsentan. The patient attested to the monthly testing prior to each dispensing, consistent with the REMS requirements, however the laboratory values were not provided. Figure 3 provides liver biochemistry studies (ratio to ULN) over time.

Figure 3. Liver Biochemistry Studies (Ratio to ULN) for Case (b) (6)



Abbreviations: ULN = upper limit of normal

Source: S-005 Information Request Response, dated March 3, 2025
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RGD = rare glomerular disease ULN = upper limit of normal

Appendix D. Relevant Regulatory Communications

Hepatotoxicity: Interactions with the Applicant since approval

- Type B meeting; refer to the Type B Briefing Document, dated May 29, 2024, and Written Response, dated July 19, 2024, to discuss hepatotoxicity risk and REMS
- Type D meeting, refer to the Type D Briefing Document, dated August 1, 2024 and Written Response, dated September 19, 2024, to discuss hepatotoxicity risk and REMS

Embryofetal toxicity: Interactions with the Applicant since approval

- REMS Modification Notification, dated March 11, 2025, sent to the Applicant to remove the EFT risk from the REMS; this action is based upon a review of postmarketing data, reassessment of the risk, and implications for the REMS and labeling provided by DCN, DPMH, and DRM (refer to the reviews in DARRTS).
- Supplement amendment, dated May 19, 2025, to remove the EFT risk from the REMS

Appendix E. Sparsentan Exposure Data

Data Source		
Clinical Studies	Total patients treated (n)[a]	1,599

	Double-blind Period (n)[b]	680
	Open-label Period (n)[c]	612
	Total exposure (patient-years)[d]	2,217.8
	Mean treatment duration (days)	506
	Patients treated >337 days (n)	658
	Patients treated >1,008 days (n)	355
Postmarketing REMS	Total REMS patients exposed (n) [e]	2,029
(as of August 16, 2024)	Patients on drug >6 months (n)	902
	Patients on drug >12 months (n)	294

Source: S-005 REMS Major Mod Data Pkg, dated October 21, 2024
Note: Data cutoff dates were 01Aug2024 for PROTECT, DUPLEX, EPPIK, SPARTAN, and SPARTACUS. Data for DUET is based on the database lock date of 08 May 2024.
[a]All Sparsentan column includes patients who received at least 1 dose of sparsentan during any treatment period for PROTECT, DUET, DUPLEX, EPPIK, SPARTAN, and SPARTACUS
[b] OLE period from PROTECT, DUET, and DUPLEX
[c]OLE Sparsentan column includes patients who received at least 1 dose of sparsentan during open label treatment periods in PROTECT, DUPLEX, and DUET.
[d] Total Patient-Years are calculated as sum of total number of dosed days across all patients/365 days.
[e] Includes previously exposed patients from clinical trials

Appendix F. Applicant's Market Research on Impact of Monthly Testing

(b) (4), survey of nephrologists who managed > 2 IgAN patients and have > 1 patient for whom they considered Filspari in the past 6 months.

- 113 nephrologists completed the survey from academic (31%) and community (69%) settings in the US
- The frequency of blood monitoring impacts patients at 3 separate areas in the decision to prescribe or take FILSPARI.
    1. Impact on physician decision to initially discuss FILSPARI with a patient.
    2. Impact on patient willingness to accept therapy when the physician does offer it as an option.
    3. Impact on patient retention.

Appendix G. Sparsentan NDA 216403 Supp-005 Mid-Cycle Presentation, DILI Team, Division of Hepatology and Nutrition, April 3, 2025

Request for REMS Modification
NDA 216403—FILSPARI (sparsentan); IgAN

DHN DILI Team Review Update

Apr 3, 2025

NDA216403 (216403 - 0138 - (232) - 2024-11-18 - ORIG-1 /REMS/SPL Draft) - FILSPARI Final REMS SPL (24 Sep 2024)

[redacted]

(b) (4)

Crux of their argument

- Monitoring every three months during study protocols was adequate.

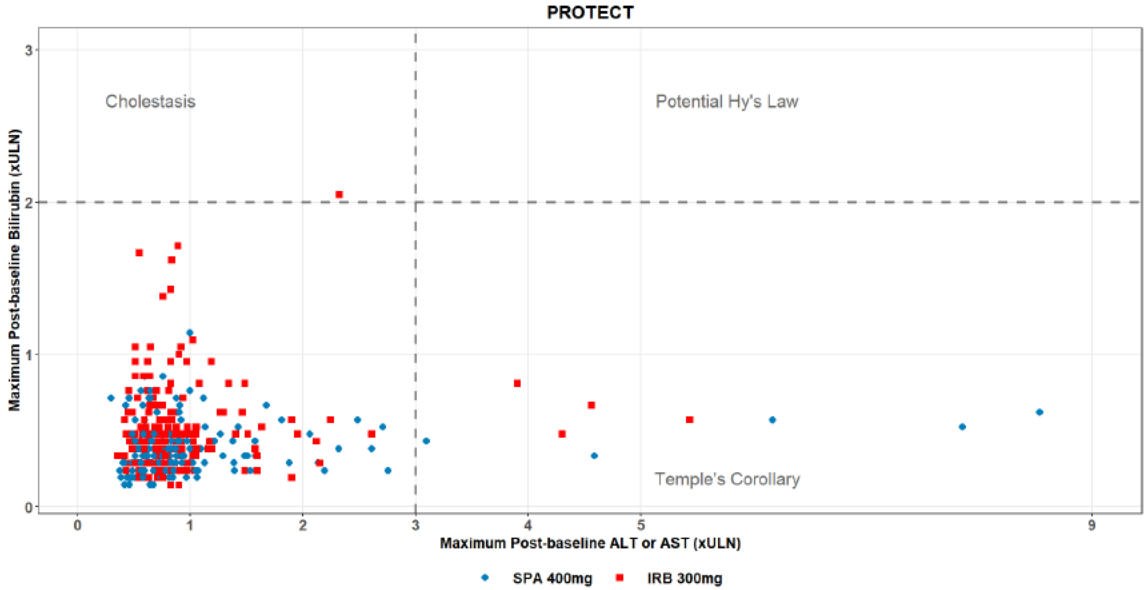
  "Given the transaminase elevations were identified and well managed in the clinical trials when testing was 12 weeks apart, the data support quarterly monitoring to manage the risk without placing additional burden on patients and physicians through more frequent testing."

  NDA216403 (216403 - 0098 - (154) - 2024-04-01 - SUPPL-3 (Efficacy) /REMS/Amendment) - S-003 REMS Modification Request (25 Mar 2024) (#7)

- Have not seen severe liver injury in REMS thus far.

Review of DILI Risk

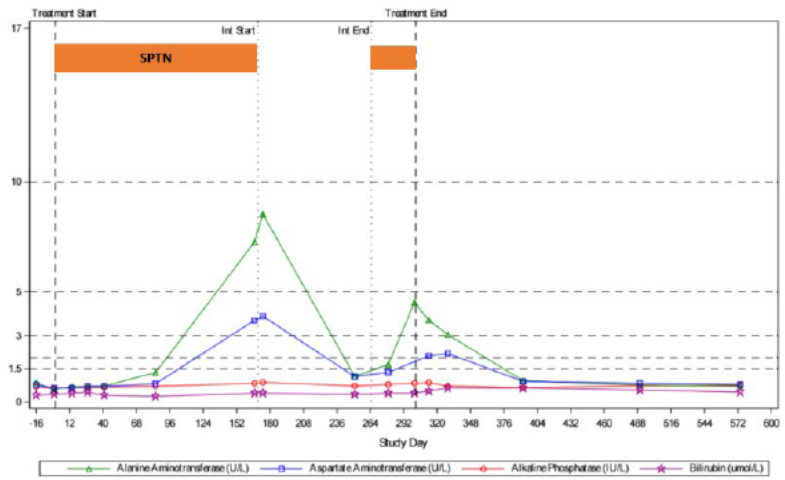
- Hepatocellular
- No Hy's Law cases but one with hyperbilirubinemia
- Some imbalance in Temple's Corollary at >5x ULN
- Three positive rechallenges.



#	ID	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)
1	(b) (6)	3	NA	021IGAN17001 PROTECT	47	M	White	No	168	-85	805	480	104	1.6	23.7	14.1
2		3	NA	021IGAN17001 PROTECT	27	M	White	No	257	-118	277	89	104	0.6	8.1	2.6
3		3	NA	021IGAN17001 PROTECT	55	M	White	No	166	-2	350	144	113	0.8	9.5	3.9
4		3	NA	021IGAN17001 PROTECT	54	M	Latinx	No	406	-6	188	76	104	0.3	5.5	2.2
5		3	NA	021FSGS16010 DUPLEX	42	M	Latinx	No	82	-22	759	504	104	0.6	22.3	14.8
				Mean	*45*				*216*	*-47*	*476*	*259*	*106*	*0.8*	*13.8*	*7.5*
				Std dev	*10.18*				*110*	*47*	*256*	*192*	*4*	*0.4*	*7.6*	*5.7*
				Median	*47*				*168*	*-22*	*350*	*144*	*104*	*0.6*	*9.5*	*3.9*
				Min	*27*				*82*	*-118*	*188*	*76*	*104*	*0.3*	*5.5*	*2.2*
				Max	*55*				*406*	*-2*	*805*	*504*	*113*	*1.6*	*23.7*	*14.8*

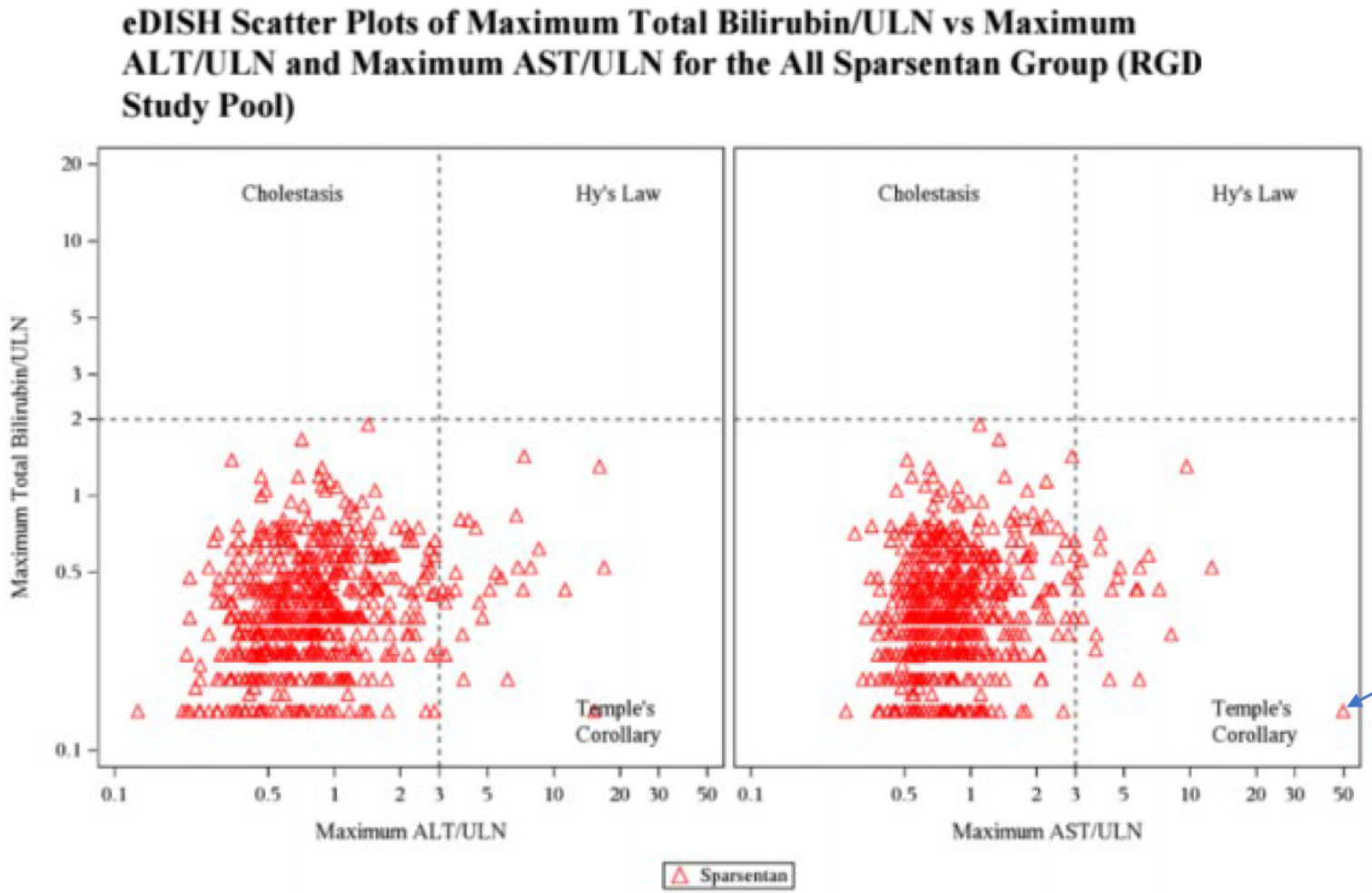
*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^For R-value calculations, ULN of 104 U/L for ALP imputed when peak ALP remained normal
NA = not applicable

Figure 3: Liver Biochemistry Studies (Ratio to ULN) for Subject (b) (6)



All figures from DILI Team Consult review, Sep 15, 2022

R2IR—Mar 3, 2025



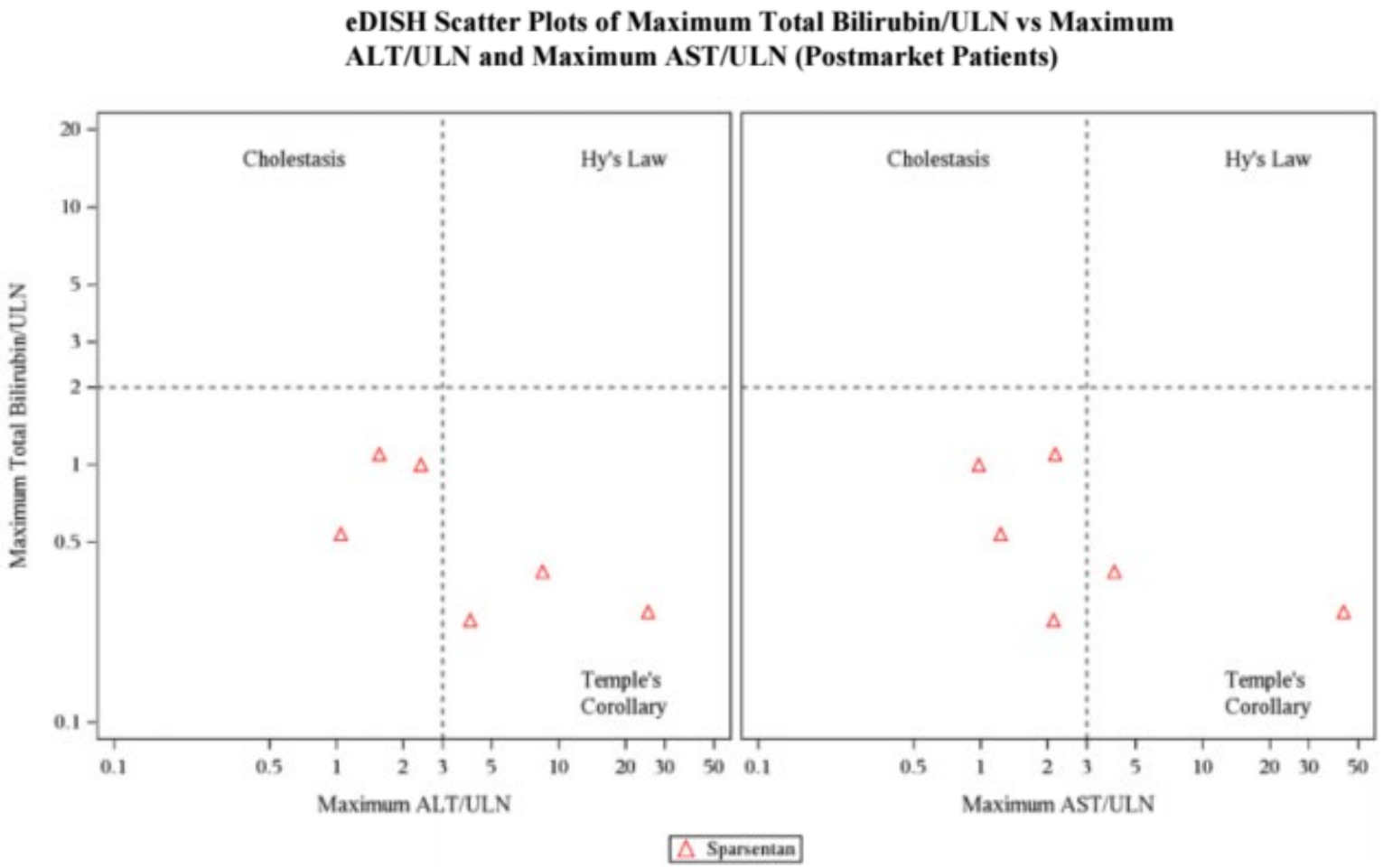
Case of "COVID pneumonia"

NDA216403 (216403 - 0142 - (245) - 2025-03-17 - SUPPL-5 (Efficacy) /REMS/Response to IR) - S-005 Information Request #1 (03 Mar 2025) Response - REMS (#2)

REMS exposure numbers
(R2IR censor date: Aug 16, 2024)

- 2029 REMS patients exposed (1041 patient-years)
- 902 on drug for > 6 mo.
- 294 on drug for >12 mo.

Post-Market eDISH plots



Liver blood test data only available for those with abnormal values.

Therefore, only six subjects plotted.

Seems odd to have so few out of

NDA216403 (216403 - 0142 - (245) - 2025-03-17 - SUPPL-5 (Efficacy) /REMS/Response to IR) - S-005 Information Request #1 (03 Mar 2025) Response - REMS (#3)

Case analyses

Open-label Cases with AT >3x ULN

- 20 cases
  - 9 with ATs >5x ULN
    - 3 probable
    - 5 possible/unlikely
    - 1 indeterminate

NDA216403 (216403 - 0137 - (227) - 2024-10-28 - SUPPL-5 (Efficacy) /Multiple Categories/Subcategories) - S-005 REMS Major Modification Data Package: Updated Exposure and Hepatoxicity Data (#15)

Post-Market Cases with AT >3x ULN

- 7 cases
  - 6 with ATs >5x ULN
    - 1 probable/possible
    - 5 unlikely

NDA216403 (216403 - 0137 - (227) - 2024-10-28 - SUPPL-5 (Efficacy) /Multiple Categories/Subcategories) - S-005 REMS Major Modification Data Package: Updated Exposure and Hepatoxicity Data (#17)

ID	Causality Score*	Study	Age (yr)	Sex	Race	Hy's Law	Latency from start drug	Latency from stop drug	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak
(b) (6)	3	Post Market REMS	31-40	F	Unknown	No	216	0	1422	910	NA	0.35	NA
	3	DUPLEX OL	41-50	F	White	No	275	[474]	168	95	104	0.29	4.9
	3	DUPLEX OL	41-50	M	White	No	91	[5]	235	104	104	0.5	6.9
	3	PROTECT	41-50	F	Black AA	No	168	[90]	395	190	104	0.29	11.6

***1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate (Fontana RJ, et al. *Drug Saf*. 2009; 32:5-68.)**

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did not rise above the ULN

~Bracketed [ ]day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value ≤ 2

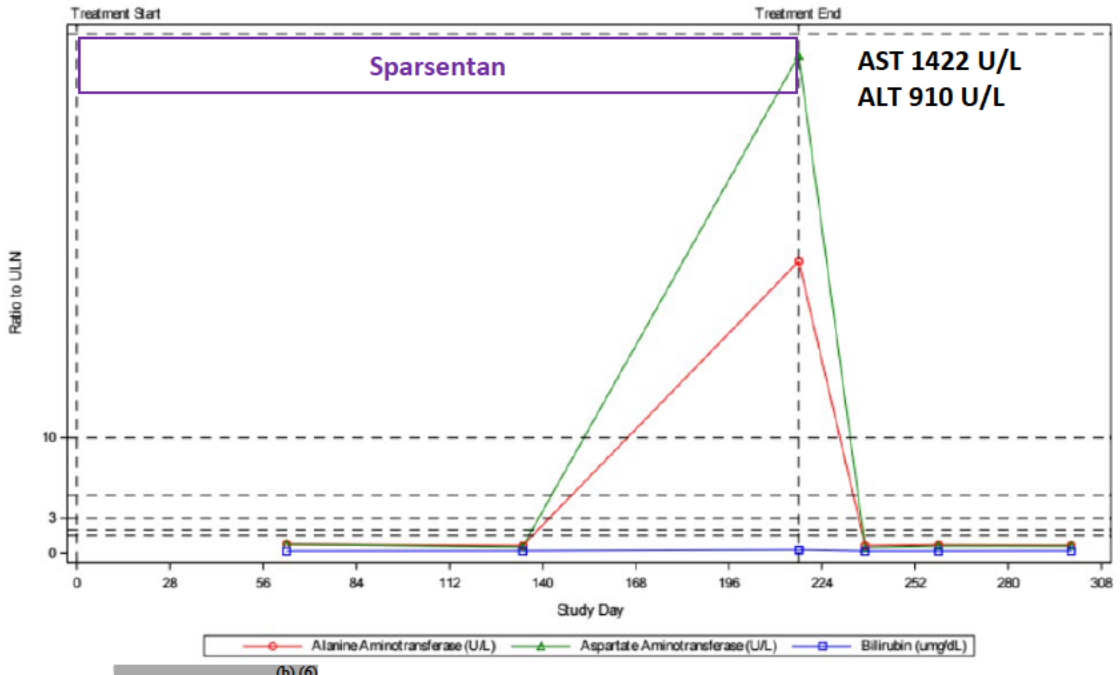
ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

Subject ID	Study	Treatment Arm	Latency (Days on Sparsentan)	Criteria for Liver-Related Event
(b) (6)	DUET	DB irbesartan/OL sparsentan	294	ALT >10× ULN AST >10 × ULN

Post-market case

Figure 23: Liver Biochemistry Studies (Ratio to ULN) for Case (b) (6)



MCN (b) (6)

Narrative Category: SAE and AE of Interest			
Patient Initials:	(b) (6)	**Age Range/Sex:**	31-40 years/Female
Country:	USA	**Treatment Indication:**	IgAN
AE Report Type:	Solicited Serious	**Reporter:**	Consumer/Non-HCP

Abbreviations: AE = adverse event; HCP = healthcare provider; IgAN = immunoglobulin A nephropathy; SAE = serious adverse event; USA = United States of America

Why are there so few liver blood tests before, during, and after this injury?

Wasn't this subject under the REMS? Subject is from US and AE *is* labeled as "Solicited" but listed as "Consumer/Non-HCP."
IR sent.

R2IR Mar 3, 2025, regarding the infrequency of testing for this case:

Sponsor does not know why more labs not available. Sponsor "opened an investigation."

NDA216403 (216403 - 0137 - (227) - 2024-10-28 - SUPPL-5 (Efficacy) /Multiple Categories/Subcategories) - S-005 REMS Major Modification Data Package: Updated Exposure and Hepatoxicity Data (#117)

Proposed change in lieu of monthly liver tests

Summary

- No severe liver injuries identified
- Number exposed is robust.
- Some concerns about under-reporting or incomplete capture of data.

Recommendations

- Allow monitoring to go to q 12 weeks from Day 1.

(b) (4)

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/s/

SELENA D DECONTI
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 23, 2025

To: Anna Park, Regulatory Project Manager, Division of Cardiology and Nephrology (DCN)

Austin H. Hu, Medical Officer, DCN

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP
Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for FILSPARI® (sparsentan) tablets, for oral use

NDA: 216403, S-005

Background:
In response to DCN's consult request dated 7/9/2025, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide (MG) for supplement 5 for FILSPARI® (sparsentan) tablets, for oral use. This supplement provides for REMS major modification and corresponding labeling updates.

PI/MG:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on 7/15/2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed MG and comments were sent under separate cover on 7/23/2025.

Thank you for your consult. If you have any questions, please contact Koung Lee at 240-402-8686 or Koung.lee@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 23, 2025
To:	Anna Park, MS, RPh, RAC Senior Regulatory Health Project Management **Division of Cardiology and Nephrology (DCN)**
Through:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FILSPARI (sparsentan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216403
Supplement Number:	S-005
Applicant:	Travere Therapeutics, Inc.

1 INTRODUCTION

On October 28, 2024, Travere Therapeutics, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 216403/S-005 for FILSPARI (sparsentan) tablets. With this submission, the Applicant proposes a Risk Evaluation and Mitigation Strategy (REMS) Major Modification to the Prescribing Information (PI) and Medication Guide (MG) to change the liver testing frequency from "monthly for 12 months, then every 3 months during treatment" to "every 3 months during treatment."

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on July 11, 2025, and July 9, 2025, respectively, for DMPP and OPDP to review the Applicant's proposed MG for FILSPARI (sparsentan) tablets.

2 MATERIAL REVIEWED

- Draft FILSPARI (sparsentan) tablets MG received on October 28, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 15, 2025.
- Draft FILSPARI (sparsentan) tablets PI received on October 28, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 15, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

HELEN K YOUNG
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KOUNG U LEE
07/23/2025 11:26:55 AM

LAURIE J BUONACCORSI
07/23/2025 11:46:10 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 12, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 216403/S-005
Product Name, Dosage Form, and Strength:	Filspari (sparsentan) tablets, 200 mg and 400 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Travere Therapeutics, Inc.
FDA Received Date:	October 28, 2024
TTT ID #:	2024-11694
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

Travere Therapeutics, Inc. submitted an Efficacy Supplement for Filspari (sparsentan) tablets to update the REMS liver testing frequency from "monthly for the first 12 months, then every 3 months during treatment" to "every 3 months during treatment". We reviewed the proposed Filspari Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Filspari (sparsentan) was approved on February 17, 2023 under NDA 216403 as an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression. It is currently available as 200 mg and 400 mg tablets.

1.2 REGULATORY HISTORY

Travere Therapeutics, Inc. submitted a proposed REMS Major Modification, as part of supplement S-003, to change the liver testing frequency from "monthly for 12 months, then every 3 months during treatment" to "every 3 months during treatment". This proposed REMS modification was discussed with the Agency in a subsequent Type B meeting held on July 19, 2024.[a] Travere Therapeutics submitted a Type D Written Response Only (WRO) request on August 01, 2024 to reach alignment with the Agency on the data package necessary to support review of the proposed modification to liver monitoring within the REMS.

Thus, Travere Therapeutics, Inc. submitted supplement S-005 on October 28, 2024 which includes the data package consistent with the Agency's advice received in the Type B Meeting.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

Our evaluation of the proposed Filspari Prescribing Information (PI) and Medication Guide (MG) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

[a] Sponsor's Minutes: NDA 216403. Filspari (sparsentan). Type B Meeting. San Diego (CA): Travere Therapeutics, Inc.; 2024 JUL 26. Available from: \\CDSESUB1\EVSPROD\nda216403\0119\m1\us\type-b-mtg-rems-mod-sponsor-minutes.pdf

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Filspari received on October 28, 2024 from Travere Therapeutics, Inc..

Table 2. Relevant Product Information for Filspari	
Initial Approval Date	2/17/2023
Active Ingredient	sparsentan
Indication	the treatment of primary immunoglobulin A nephropathy (IgAN) to preserve kidney function
Dosage Form	tablets
Strength	200 mg and 400 mg
Route of Administration	Oral
Dose and Frequency	Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily
How Supplied	FILSPARI is supplied in bottles of 30 film-coated tablets. • 200 mg tablets are film-coated, modified oval, white to off-white, debossed with “105” on one side and plain on the other side, available in bottles of 30 tablets with child-resistant caps (NDC 68974-200-30). • 400 mg tablets are film-coated, modified oval, white to off-white, debossed with “021” on one side and plain on the other side, available in bottles of 30 tablets with child-resistant caps (NDC 68974-400-30).
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store FILSPARI in its original container.
Container Closure	40-cubic centimeter (cc), wide-mouth, round, white, high-density polyethylene (HDPE)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Filspari labels and labeling submitted by Travere Therapeutics, Inc..

- Prescribing Information received on October 28, 2024, available from \\CDSESUB1\EVSPROD\nda216403\0137\m1\us\filspari-annot-uspi-20241011.pdf
- Medication Guide received on October 28, 2024, available from \\CDSESUB1\EVSPROD\nda216403\0137\m1\us\filspari-annot-med-guide-20241011.pdf

APPEARS THIS WAY ON ORIGINAL

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On February 7, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, 'filspari', 'sparsentan', and '216403'. Our search identified 1 previous review[c] since the date of our last search on June 11, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[c] Black, S. Label and Labeling Review for Filspari (NDA 216403/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 06. TTT ID No.: 2024-8836.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216403
Supplement Number, Date Received	Supplement 5 received October 28, 2024 (sequence 137) and amended May 19, 2025 (sequence 155), and August 5, 2025 (sequence 164)
Action Date	August 28, 2025
Nexus TTT #	2024-11696
Reviewer Names	Theresa Ng, PharmD, BCPS, and Derrick D. Beasley, MS, MPH (DRM) Yanick Elame, PharmD, Division of Mitigation and Medication Error Surveillance (DMAMES)
Team Leaders	Kathryn Marwitz, PharmD, MPH (DMAMES) Yasmeen Abou-Sayed, PharmD (DRM)
Associate Division Directors	Page Crew, PharmD, BCPS, MPH (DMAMES) and Suzanne Robottom, PharmD (DRM)
Review Completion Date	August 21, 2025
Subject	Review of proposed Major REMS Modification
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics Inc.
Therapeutic Class	Endothelin and angiotensin II receptor antagonist
Dosage Form(s)	200 mg and 400 mg oral film-coat tablets

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This is a review of the proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Filspari (sparsentan), NDA 216403, submitted by Travere Therapeutics (Travere) on October 28, 2024, and amended on May 19, 2025, and August 5,2025.

The REMS for Filspari was originally approved on February 17, 2023, to mitigate the risk of embryo-fetal toxicity (EFT) and hepatotoxicity, with the most recent REMS modification approved on September 5, 2024.

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

Travere initially submitted efficacy supplement (S-005) proposing changes to the label and corresponding modification to the REMS to update the liver monitoring frequency from "monthly for 12 months, then every 3 months during treatment", as currently approved, to "every 3 months during treatment", citing clinical data showing 3-month intervals were sufficient, potential improvements to patient access, and successful REMS performance results from the REMS Assessments.

During the S-005 review, the Agency issued a REMS Modification Notification Letter (RMNL) on March 11, 2025, requiring the removal of embryo-fetal toxicity (EFT) risk from the REMS and corresponding safe use conditions, based on safety re-evaluation of the endothelin receptor antagonist (ERA) drug class.[1,2] Travere subsequently amended the proposed REMS in S-005 on May 19, 2025, removing the EFT requirements while maintaining the proposed changes to the liver monitoring frequency and increasing outpatient pharmacy dispensing from 30 to a 90-day supply.

DRM finds the proposed changes acceptable and recommends approval of the REMS modification.

There are no changes to the timetable for submission of assessments of the REMS.

The Assessment Plan was revised to remove all EFT-related metrics and add revised categories for Safe Use Behavior and Health Outcomes related to hepatotoxicity.

1 Introduction

This review evaluates the proposed modification to the REMS for Filspari (sparsentan), new drug application (NDA) 216403, submitted by Travere on October 28, 2024, and amended on May 19, 2025, 2025, and August 5, 2025.

Travere initially proposed changing the liver monitoring frequency from "monthly for 12 months then every 3 months" to "every 3 months throughout treatment", citing clinical data showing 3-month intervals were sufficient to capture and mitigate any risk posed by elevated liver enzymes, improved healthcare system burden and patient access considerations, and successful REMS performance in the latest REMS assessment.

During the S-005 review, the Agency completed a re-evaluation of embryo-fetal toxicity (EFT) risk in the endothelin receptor antagonist (ERA) drug class.[2] The Division of Cardiology and Nephrology (DCN) and Division of Pediatric and Maternal Health (DPMH) determined that EFT risk could be adequately communicated through labeling and the REMS is no longer necessary to ensure the benefits of the drugs outweigh the risk of EFT in the ERA drug class.[3] The REMS Oversight Committee (ROC) concurred with the proposal to eliminate the REMS requirement for EFT across the ERA drug class.[4,5] Consequently, the Agency issued a REMS Modification Notification Letter (RMNL) on March 11, 2025, requiring the removal of the EFT risk from the Filspari REMS.[1]

In response to the RMNL, Travere amended the REMS modification in S-005 on May 19, 2025, to remove EFT risk and requirements while maintaining proposed changes to the liver monitoring frequency. The modifications are reflected throughout the REMS Document, materials, website, and Supporting Document. The assessment plan was updated to include additional metrics for safe-use behavior related to liver testing and health outcomes related to hepatotoxicity.

2 Background

2.1 PRODUCT INFORMATION

Filspari (sparsentan) is an angiotensin II (AT_1R) and endothelin (ET_AR) receptor antagonist (ERA) that received accelerated approval on February 17, 2023, and full approval on September 5, 2024, to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.[6,7] Filspari is available as 200 mg and 400 mg oral film-coated tablets. The recommended dose is 200 mg once daily orally for 14 days, then increased to 400 mg daily as tolerated.

Filspari was approved with a REMS to ensure that the benefits of the drug outweigh the risks of hepatotoxicity and embryo-fetal toxicity.

The goal of the Filspari REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari:

- Objective 1: Monitor for elevations in liver enzymes in patients exposed to Filspari
- Objective 2: Ensure that patients who can become pregnant are not pregnant before initiating Filspari
- Objective 3: Minimize exposure in patients who may become pregnant while taking Filspari

The most recently approved REMS (September 5, 2024) include elements to assure safe use (ETASU) consisting of prescriber certification (ETASU A), pharmacy certification (ETASU B), documentation of safe use conditions (ETASU D), and patient monitoring (ETASU E), along with an implementation system, and a timetable for submission of assessments. A postmarketing requirement (PMR) is also necessary to further characterize hepatotoxicity risk.

3 Filspari REMS Assessment

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) completed their review of the 1- year Filspari REMS Assessment Report on August 29, 2024.[8] Based on the totality of the information contained within the 1- year Assessment Report, DMAMES concluded that the goals of the Filspari REMS were met. The following table provides a brief summary of the Filspari REMS assessment results.

Table 1: 1-Year Filspari REMS Goal and Objectives Assessment Results

REMS Goal:		
The goal of the Filspari REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari.		
REMS Objectives	Select Assessment Metrics	Targeted Threshold
Objective 1: monitor for elevations in liver enzymes	99.97% of the prescriptions dispensed to patients by outpatient pharmacies were dispensed following confirmation from a certified pharmacy that liver testing	≥98%

in patients exposed to Filspari	was performed when required or that the prescriber authorized the refill prior to each dispense	
Objective 2: patients who can become pregnant are not pregnant before initiating Filspari	99.14% of patients (who can become pregnant) had documentation of a negative pregnancy test on the **Patient Enrollment Form** prior to treatment initiation	≥99%
Objective 3: minimize exposure in patients who may become pregnant while taking Filspari	99.39% of dispenses were associated with a confirmation from a certified pharmacy that monthly pregnancy testing was performed, or the prescriber authorized the refill prior to each dispense	≥98%

The 2-Year REMS Assessment report, submitted on February 14, 2025,[9] is currently under review. The 2-year REMS assessment review focuses on metrics related to mitigating the risk of hepatotoxicity and preliminary results are consistent with the determination of the 1-year REMS assessment review.

3.1 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- 10/28/2024: Travere submitted efficacy supplement, S-005, to extend the frequency of liver monitoring from monthly for the first 12 months, then quarterly, thereafter, to quarterly during treatment with Filspari (eCTD seq no. 137).
- 3/11/2025: The Agency issued an RMNL to remove EFT risk from the Filspari REMS.
- 5/12/2025: Travere submitted (b) (4) (b) (6)
- 5/15/2025: Advice Letter issued to Travere to submit a revised REMS, reflecting removal of EFT risk, proposed change in liver monitoring frequency, and updated labeling to reflect these changes. (b) (4) (b) (4)
- 5/19/2025: Travere submitted an amendment to S-005 in response to the Agency's General Advice Letter, dated May 15, 2025 (eCTD seq no. 155).
- 7/17/2025: Information request (IR) issued to Applicant to retain inpatient pharmacy 30-days' supply dispensing limit and for outpatient pharmacy to maintain a one-time authorization to dispense a greater than 90-days' supply, if needed.
- 7/28/2025: The Agency issued an IR to clarify that healthcare providers are required to counsel patients on the risk of hepatotoxicity if they are not complying with the required liver testing in the REMS Document. The Applicant is to incorporate this edit to all impacted REMS materials in their forthcoming REMS amendment submission.
- 8/5/2025: Applicant submitted amendment in response to the Agency's July 17, 2025, and July 28, 2025, IRs (eCTD seq no. 164).

4 Risk Assessment and Safe-Use Conditions

Travere submitted an efficacy supplement (S-005) to change the liver testing cadence to quarterly during treatment (previously every month for the first 12 months, then every 3 months during treatment). This change would impact the REMS participant requirements for liver monitoring, verification, and counseling.

Additionally, during the review of S-005, the Agency issued an RMNL on March 11, 2025, to remove the risk of EFT from the Filspari REMS.

The following provides information to support changes to the REMS requirements for the hepatotoxicity and EFT risks.

4.1 Hepatotoxicity

In S-005, Travere submitted updated exposure data and case level information on elevated transaminases from ongoing clinical studies and postmarketing experience. DCN consulted the Division of Hepatology and Nutrition (DHN) on November 20, 2024, to review the proposal to change the liver monitoring frequency from monthly to every 3 months, noting that a previous proposal in S-003 was rejected due to inadequate exposure data.[10] (b) (4)

(b) (4)

(b) (4)

DHN's review identified 27 patients with transaminase elevations >3× ULN and/or serious liver events since approval through August 1, 2024 (20 patients during open-label clinical trials[a] (PROTECT n=6; DUPLEX n=10; DUET n=4) and 7 from the REMS population). Among 15 cases with transaminase elevations >5× ULN, there were 4 probable drug-induced liver injury cases, 10 possible/unlikely cases, 1 indeterminate case, and no cases meeting Hy's Law criteria. While these postmarket findings were consistent with pre-approval data, DHN noted potential under-reporting concerns since liver testing results were only available from REMS participants reporting abnormal results.

Despite limited data collection concerns, DHN and DCN support the quarterly liver monitoring change based on the absence of Hy's Law cases, consistency with PROTECT[b] study safety data and maintaining REMS safeguards which require liver testing verification before dispensing.[13] The hepatotoxicity risk remains as a Boxed Warning with this updated monitoring frequency, and corresponding modification to the REMS.

4.2 Embryofetal Toxicity (EFT)

On March 11, 2025, the Agency issued an RMNL directing Travere to remove the EFT risk from the Filspari REMS. This decision followed a re-analysis of human fetal outcomes from 2001 to 2024 after exposure to ERA drugs, with DCN and DPMH concluding that reported data did not show congenital malformation patterns consistent with animal studies.[2] The ROC concurred with removing EFT risk from REMS for the ERA drug class, determining that labeling would adequately communicate and mitigate this risk.[4,5] DRM agreed with DCN and DPMH to remove the EFT risk from the REMS for the ERA drug class.[14]

Labeling will retain EFT risk information in a Boxed Warning and Warnings and Precautions section 5.3, informing healthcare providers that Filspari is contraindicated in pregnancy and requiring them

[a] See Integrated Review for NDA 216403, dated February 17, 2023, DARRT reference number ID: 5128407 for details of the clinical trials.

[b] PROTECT study is the primary phase 3 study in the approval of Filspari for IgAN.

to counsel patients of childbearing potential about fetal risks, exclude pregnancy before treatment initiation, ensure effective contraception use before, during, and for two weeks after discontinuation, and discontinue Filspari if pregnancy is suspected.

5 Expected Postmarket Use

Nephrologists are the primary prescribers for Filspari, which has been approved since 2023 with a REMS to mitigate hepatotoxicity and EFT risks. Extending liver monitoring frequency to quarterly and removing REMS requirements related to the EFT risk will reduce healthcare system burden and potentially improve patient access while continuing to ensure that the benefits of the drug outweigh its risks.

6 Review of Proposed REMS Modifications

Editorial changes for version control, footer notes, and formatting were made throughout the REMS, along with additional edits to the REMS materials to improve clarity and readability. Specific changes to the REMS are described below.

6.1 REMS GOALS

Following the March 11, 2025, RMNL, Travere removed the EFT risk from the REMS and updated the Filspari REMS goal and objective from:

The goal of the Filspari REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari.

Objective 1: monitor for elevations in liver enzymes in patients exposed to Filspari.

Objective 2: patients who can become pregnant are not pregnant before initiating Filspari.

Objective 3: minimize exposure in patients who may become pregnant while taking Filspari.

to:

The goal of the FILSPARI REMS is to mitigate the risk of hepatotoxicity associated with FILSPARI.

Objective 1: monitor for elevations in liver enzymes in patients exposed to Filspari.

Reviewer Comment: *We agree with the Applicant's proposed changes to the REMS goal and objective statements.*

6.2 REMS DOCUMENT

6.2.1 REMS Participant Requirements and Materials

6.2.1.1 Healthcare Provider

Travere proposed changing liver monitoring frequency requirements from monthly for the first 12 months then every 3 months, to every 3 months during treatment to align with proposed labeling updates, with added clarification requiring healthcare providers to counsel patients on hepatotoxicity risk if they are non-compliant with liver testing. Following the March 11, 2025, RMNL removing EFT risk requirements, all associated EFT requirements for healthcare providers were eliminated from the REMS, resulting in updates to the **Prescriber Enrollment Form** and removal of the **Change in Reproductive Status Form** as it is no longer required.

Reviewer Comment: *DRM agrees with the proposed healthcare provider requirement changes to correspond with labeling updates and the March 11, 2025, RMNL.*

6.2.1.2 Patients

Following the March 11, 2025, RMNL to remove the EFT risk from the REMS, patients who can become pregnant are no longer required to undergo monthly pregnancy testing or receive pharmacist counseling on the EFT risk. The two patient categories ("Patients who can become pregnant" and "Patients who cannot become pregnant") were consolidated into a single category of "Patients who are prescribed Filspari," and liver testing and pharmacist counseling requirements were changed from monthly for the first 12 months then every 3 months to every 3 months during treatment.

The **Patient Enrollment Form** and **Patient Guide** were updated accordingly to align with these changes.

Reviewer Comment: *We agree with the proposed patient requirement changes, which align with labeling changes and the March 11, 2025, RMNL. The proposed labeling updates will continue to educate healthcare providers about EFT risk and recommended actions for patients who can become pregnant.*

6.2.1.3 Inpatient and Outpatient Pharmacies

Inpatient and outpatient pharmacy requirements were updated to remove the EFT risk following the March 11, 2025, RMNL, eliminating requirements for pharmacies to verify monthly pregnancy testing and provide EFT risk counseling to patients who can become pregnant. Outpatient pharmacy verification of liver testing completion and hepatotoxicity counseling frequency was changed to initial dispense and every 3 months during treatment to be consistent with labeling updates, with dispensing limits increased to 90-day supplies for outpatient pharmacies while maintaining 30-day limits for inpatient pharmacies. Travere added clarification restricting pharmacies from distributing, transferring, loaning, or selling Filspari except to certified dispensers, with corresponding updates made to inpatient and outpatient pharmacy enrollment forms.

Reviewer Comment: *The proposed changes to pharmacy requirements are acceptable and align with proposed labeling and the March 11, 2025, RMNL. In their May 19, 2025, amendment, Travere initially proposed* (b) (4) (b) (4) *. DRM agreed with 90-day supplies for outpatient pharmacies to provide flexibility and align with changes in liver testing cadence but disagreed with* (b) (4) (b) (4)

Additionally, DRM does not agree with (b) (4) , (b) (4) (b) (4) *inpatient pharmacies will maintain 30-day supply limits upon discharge, and outpatient pharmacies will retain a one-time exception authorization for greater than 90-day supplies when authorized by certified providers, with* (b) (4) *required documentation for dispense override.*

DCN concurred with DRM's determination to allow outpatient pharmacies to dispense 90-days' supply, to maintain inpatient dispense to 30-days, and to not allow for greater than one-time override authorization for a greater than 90-day dispense.[c] *These requirements were communicated in the July 17, 2025, IR, and Travere agreed to remove them in their August 5, 2025, REMS amendment.*

[c] DeConti, Selena. Email communication dated June 2, 2025.

6.2.2 REMS Applicant Requirements and Materials

6.2.2.1 Training

Travere updated the **Prescriber and Pharmacy Guide** and the **Patient Guide** to reflect EFT risk removal, change liver testing, verification, and counseling cadence to every 3 months, and increased certified outpatient pharmacies dispense allowance to 90-day supply during treatment with Filspari.

Reviewer Comment: *We agree with these changes as they are consistent with proposed labeling updates and the March 11, 2025, RMNL noting that outpatient pharmacies may dispense 90-day supplies while inpatient pharmacies* (b) (4) *to 30-day supplies upon discharge, and outpatient pharmacies* (b) (4) *maintain one-time override authorization* (b) (4) (b) (4)

6.2.2.2 Operations

Travere updated the **REMS website** to be consistent with the March 11, 2025, RMNL by removing all EFT information and adding a pop-up alert to notify REMS participants of EFT risk removal and change in liver monitoring frequency (before initiation, and every 3 months during treatment). The REMS website reflects proposed changes in liver testing, verification, and counseling cadence along with increased outpatient pharmacy dispensing limits to 90-day supplies.

Several enhancements to the REMS website were made to improve healthcare provider assistance and REMS compliance, including allowing Office Contacts to complete patient demographics to initiate enrollment. Outpatient Pharmacy Portal enhancements include reminder messages for hepatotoxicity counseling completion, REMS verification code expiration date alerts, and tracking of last counseling date and liver testing verification to assist with compliance for initial dispense and every 3 months thereafter. Travere also added clarification restricting outpatient and inpatient pharmacies from distributing, transferring, loaning, or selling Filspari except to certified dispensers.

Reviewer Comment: *The proposed changes in the **REMS website** are acceptable and are consistent with the changes in the REMS and proposed labeling.*

6.3 REMS ASSESSMENT TIMETABLE

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

7 Supporting Document

The REMS Supporting Document was updated to include background on the current REMS modification under review and described above in this review. In addition, Travere removed EFT-associated key performance indicators and incorporated key risk messages (KRMs) for REMS participants that align with REMS goals and guide risk messaging throughout materials, along with minor revisions, formatting changes, and updated version control.

Reviewer Comment: *The REMS Supporting Document changes are acceptable and reflect proposed modifications we agreed with in the REMS Document, labeling, and March 11, 2025, RMNL. In the July 17, 2025, IR, the Agency provided KRMs for Travere to incorporate into the REMS Supporting Document, which the Applicant agreed to and included in their August 5, 2025, REMS amendment.*

8 REMS Assessment Plan

In response to the Agency's March 11, 2025, RMNL, Travere proposed removing all EFT-related metrics from their revised REMS Assessment Plan contained within the REMS Supporting Document of the May 19, 2025 REMS amendment. In addition to removing all of the EFT-related metrics from the Assessment Plan, Travere also proposed changes to a REMS compliance metric pertaining to prescriptions dispensed for greater than a 90-day supply.

DMAMES completed a review of the Assessment Plan and proposed additional revisions including further revisions to the REMS compliance metric, removal of age stratification from the REMS utilization metric, and revision of two assessment categories: Safe Use Behaviors and Health Outcomes, to be focused on hepatoxicity. Metrics in both revised assessment categories will be used to evaluate compliance with the REMS requirements and assess the effectiveness of the REMS strategies in mitigating the risk of hepatotoxicity.

The Applicant accepted all DMAMES' proposed revisions in their August 5, 2025, REMS amendment and the final agreed upon REMS Assessment Plan includes metrics under the following categories: REMS Implementation and Operations, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes, and Overall Assessment of REMS Effectiveness. The proposed metrics are necessary to evaluate if the REMS is operating as intended and meeting its goal mitigating the risk of hepatotoxicity associated with Filspari, specifically by meeting its stated objective. Finally, Travere updated and included as an appendix to the REMS Supporting Document the Assessment Plan in a tabular format.

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be addressed in the REMS Modification Approval letter.

Reviewer Comment: *DMAMES finds the Applicant's proposed REMS Assessment Plan, as amended on August 5, 2025, to be acceptable. The REMS Assessment Plan is included as an appendix in this review and will be addressed in the REMS Modification Approval Letter.*

9 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on July 16, 2025, to provide feedback on the content of the updated Filspari REMS materials. The OPDP review was completed by Koung Lee on July 29, 2025.

The OPDP recommended to align the language in the REMS materials with the final approved Prescribing Information (PI) and Medication Guide (MG) to accurately reflect the risk information and minimize promotional content. DRM incorporated these recommendations into the REMS materials. To note, the OPDP reviewer highlighted that the Applicant's proposed website included (b) (4) (b) (4) which was inconsistent with the Filspari REMS Document, Filspari REMS Inpatient Pharmacy Enrollment Form, and the Filspari REMS Prescriber and Pharmacy Guide. This feedback was communicated to the Applicant and the finalized REMS materials were revised (b) (4) (b) (4)

Reviewer Comment: *The proposed REMS materials are acceptable and align with the changes in the REMS and proposed labeling.*

10 Discussion

Filspari (sparsentan), an angiotensin II and endothelin receptor antagonist, is approved to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.[7] As a drug in the ERA drug class with known EFT and hepatotoxicity risks, Filspari was approved with a REMS requiring scheduled pregnancy and liver testing monitoring for safe use.[6]

Travere submitted S-005 on October 28, 2024, proposing to change the liver monitoring frequency requirements in the label and REMS from monthly for 12 months then every 3 months to every 3 months throughout treatment. DCN and DHN support this change based on the absence of Hy's Law cases with additional exposure, consistency between postmarket experience and clinical trial safety data, and maintaining the REMS safeguards requiring liver testing verification before dispensing. During the review, on March 11, 2025, the Agency issued an RMNL directing removal of EFT risk from the Filspari REMS based on DCN and DPMH's re-analysis that labeling would adequately communicate EFT risk across the ERA drug class. Both ROC and DRM concurred with removing the EFT risk from all ERA REMS.

Travere submitted REMS amendments on October 28, 2024, May 15, 2025, and August 5, 2025, removing the EFT risk and the **Change in Reproductive Status Form** from the Filspari REMS, while maintaining EFT communication in labeling (Boxed Warning, pregnancy contraindication, and Warnings and Precautions on the risk of EFT with advice for HCPs to counsel patients who can get pregnant on effective contraception and to avoid pregnancy before, during, and 2 weeks after treatment discontinuation). The proposal to increase dispensing from 30 to 90 days is acceptable for outpatient pharmacies (b) (4) (b) (4). Similarly, the proposal for (b) (4) (b) (4) was not acceptable and we agree with maintaining a one-time authorization with documentation of reason for override (b) (4) (b) (4)

REMS website enhancements include improved outpatient pharmacy portal functions to increase compliance through addition of verification code expiration dates, hepatotoxicity counseling reminder, and clarification on restrictions on distributing Filspari only to certified dispensers. Office Contacts will be allowed to initiate patient enrollment to reduce administrative burden on healthcare providers. The REMS website will also be updated to alert REMS participants about EFT risk removal and change in liver monitoring frequency. Travere incorporated KRMs throughout the REMS materials and revised the Assessment Plan to remove EFT metrics, to revise Safe Use Behavior and Health Outcomes metrics to better assess compliance and hepatotoxicity risk mitigation.

11 Conclusions and Recommendations

DRM finds the proposed REMS modification for Filspari (sparsentan) as submitted on August 5, 2025, acceptable. The REMS materials were amended to be consistent with the revised REMS document. DRM recommends approval of the REMS Modification for Filspari, received on October 28, 2024 and last amended on August 5, 2025, and appended to this review.

The DMAMES has reviewed the REMS Assessment Plan and finds it acceptable as appended. The timetable for submission of assessments of the REMS remains the same as that approved on February 17, 2023.

The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised to be consistent with the REMS Modification for Filspari and will be included in the REMS Modification Approval letter.

12 References

1. Wachter L. DCN. REMS Modification Notification Letter, dated March 11, 2025.

2. DeConti S. DCN. Safety Memorandum. Elimination (or Modification) of the Risk Evaluation and Mitigation Strategies (REMS) for products in the Endothelin Receptor Antagonist (ERA) pharmacologic class for embryofetal toxicity risk., dated February 28, 2025. .

3. Wachter L. DCN. REMS Memoradum REMS Modification: Release of REMS requirement, dated March 11, 2025.

4. REMS Oversight Committee (ROC) Meeting Minutes, November 18, 2024.

5. REMS Oversight Committee (ROC) by Email, December 19, 2024.

6. Park A. DCN. Accelerated Approval Letter for Filspari NDA 216403, dated February 17, 2023.

7. Park A. DCN. NDA 216403 Supplemental Approval (S-003), dated September 5, 2024.

8. Elame Y. DMAMES. Review of the 1-year (1st) Filspari Risk Evaluation and Mitigation Strategy (REMS) Assessment Report, dated August 29, 2024.

9. Travere. REMS 24-Month Assessment Report, dated February 14, 2025.

10. Park A. DCN. NDA 216403/S-003 Type B Meeting Comments, dated July 1, 2024. DARRTS Reference ID: 5406057.

11. Travere. Filspari S-005 REMS Amendment, dated May 12, 2025 (eCTD seq. no. 154).

12. Wachter L. DCN. NDA 216403. Supplement 3 General Advice Letter, dated May 15, 2025. DARRTS Reference ID: 5591830.

13. DeConti S. DCN. Draft Sparsentan NDA 216403 S-005 Clinical Memo, dated July 27, 2025.

14. Caruth B. ERA REMS Modification Rationale Review, dated March 6, 2025.

13 Appendix

The following materials are part of the Filspari REMS

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. [Patient Enrollment Form]

Pharmacy:

3. Outpatient Pharmacy Enrollment Form
4. Inpatient Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

5. Prescriber and Pharmacy Guide

Patient:

6. Patient Guide

Pharmacy

7. Prescriber and Pharmacy Guide

Other Materials

8. REMS website

13.1 Assessment Plan

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

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)

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 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.

61 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

THERESA N NG
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DERRICK D BEASLEY
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YANICK E ELAME
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KATHRYN K MARWITZ
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YASMEEN I ABOU-SAYED
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ZACHARY A OLESZCZUK on behalf of PAGE E CREW
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SUZANNE B ROBOTTOM
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Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216403
Supplement Number, Date Received	Supplement 005 received October 28, 2024 (sequence 137), amended on May 19, 2025 (sequence 155)
Action Date	August 28, 2025
Nexus TTT #	2024-11696
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, and Derrick D. Beasley, MS, MPH, DRM
Team Leader(s)	Yanick Elame, PharmD, DMAMES Kathryn Marwitz, PharmD, MPH, DMAMES Yasmeen Abou-Sayed, PharmD, DRM
Associate Division Director(s)	Page Crew, PharmD, MPH, BCPS, DMAMES Suzanne Robottom, PharmD, DRM
Review Completion Date	July 17, 2025
Subject	Review of proposed Major REMS Modification
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics Inc.
Therapeutic Class	Endothelin and angiotensin II receptor antagonist
Dosage Form(s)	200 mg and 400 mg oral film-coated tablets

TABLE OF CONTENTS

1. Introduction

This review evaluates the proposed modification to the REMS for Filspari (sparsentan), NDA 216403, submitted by Travere on October 28, 2024.

Filspari is an endothelin and angiotensin II receptor antagonist approved to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

Filspari received accelerated approval on February 17, 2023, followed by full approval on September 5, 2024. Filspari was approved with a REMS to ensure that the benefits of the drug outweigh the increased risks of hepatotoxicity and embryo-fetal toxicity (EFT).

Travere submitted an efficacy supplement and REMS modification (S-005) proposing modification to the label and REMS to change the liver monitoring frequency from "monthly for 12 months, then every 3 months during treatment", as currently approved, to "every 3 months during treatment". The Applicant provided the following rationale for extending the liver monitoring frequency:

- data from the clinical program showed a 3-month frequency was sufficient to capture and mitigate any risk posed by elevated liver enzymes,
- potential effects on patient access to the drug and on burden of the healthcare delivery system, and
- most recent REMS assessment showed that the Filspari REMS has fully functioned as designed and met or exceeded operational thresholds.

During the course of the review, the Agency issued a REMS Modification Notification Letter (RMNL) on March 11, 2025 to the Applicant to remove the risk of EFT from the Filspari REMS[1] based on findings from a safety re-evaluation of the EFT risk in the endothelin receptor antagonist (ERA) drug class,[2] Travere submitted an amendment to S-005 on May 19, 2025, to remove the risk of EFT along with the proposed changes in liver testing cadence.

This interim review discusses the proposed REMS submitted on May 19, 2025.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 10/28/2024: Travere submitted efficacy supplement, S-005, to extend the frequency of liver monitoring from monthly for the first 12 months, then quarterly, thereafter, to quarterly during treatment with Filspari. S-005 included a REMS modification to align the changes to liver testing cadence in the REMS with the PI. (eCTD seq no. 137).
- 3/11/2025: the Agency issued a REMS Modification Notification Letter for Filspari, NDA 216403 to inform the Applicant that a REMS is no longer necessary for the risk of EFT and to submit a REMS modification to release the risk of EFT in the REMS.
- 5/12/2025: Travere submitted [redacted] (b) (4)
- 5/15/2025: Advice Letter sent to Travere [redacted] (b) (4). The Applicant was instructed to submit a revised REMS, reflecting the removal of the risk of EFT and the proposed change for the

required liver monitoring to every 3 months during treatment along with revised labeling to reflect these changes.

- 5/19/2025: Travere submitted a REMS amendment to S-005 in response to the Agency's General Advice Letter, dated May 15, 2025 (eCTD seq no. 155).

3. Review of Proposed REMS Modification

Editorial changes related to version control, footer notes, and formatting were made throughout the REMS. Specific changes to the REMS are described below.

3.1. REMS Goals

The Filspari REMS goal and objective were updated from:

The goal of the Filspari REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari.

Objective 1: monitor for elevations in liver enzymes in patients exposed to Filspari.

Objective 2: patients who can become pregnant are not pregnant before initiating Filspari.

Objective 3: minimize exposure in patients who may become pregnant while taking Filspari.

to:

The goal of the FILSPARI REMS is to mitigate the risk of hepatotoxicity associated with FILSPARI.

Objective 1: monitor for elevations in liver enzymes in patients exposed to Filspari.

Reviewer Comment: *We agree with the proposed changes to the REMS goal and objective as they align with the required modification communicated in the March 11, 2025, RMNL to remove the risk of EFT in the REMS.*

3.2. REMS Requirements

3.2.1. REMS Participant Requirements and Materials

3.2.1.1. Healthcare Provider

As part of the REMS, healthcare providers (HCPs) no longer are required to assess pregnancy status, monitor reproductive status, and provide counseling on effective contraception in patients who can become pregnant. Additionally, the required frequency of liver function monitoring was changed to every 3 months during treatment (previously monthly for the first 12 months, then every 3 months during treatment).

The **Prescriber Enrollment Form** was updated to reflect the removal of the EFT risk and change in liver testing frequency and aligns with the proposed updates to labeling. The **Change in Reproductive Potential Status Form** is no longer necessary and was removed.

Reviewer Comment: *We agree with the proposed changes. The updates were made to align with the changes in the REMS Document and the RMNL issued on March 11, 2025. The proposed labeling updates will inform HCPs that Filspari is contraindicated in pregnancy, to counsel patients who can get pregnant*

on the potential risk to the fetus, and use effective contraception prior to initiating, during treatment, and for two weeks after treatment discontinuation.

3.2.1.2. Patients

As part of the REMS, patients who can get pregnant are no longer required to have monthly pregnancy testing and receive counseling by pharmacies on the risk of serious birth defects. The requirement to get liver testing and receive counseling by the outpatient pharmacy was changed to every 3 months (previously every month for the first 12 months, then every 3 months during treatment). The **Patient Enrollment Form** was updated to reflect these changes.

Reviewer Comment: *We agree with the proposed changes. These changes align with the changes in the REMS Document and the RMNL issued on March 11, 2025. As noted in 3.2.1.1, labeling updates will inform HCPs on the risk of EFT and actions needed in patients who can get pregnant.*

3.2.1.3. Inpatient and Outpatient Pharmacies

The inpatient and outpatient pharmacy enrollment forms were updated to reflect the removal of information associated with the risk of EFT in the REMS. Specifically, attestations requiring pharmacies to verify completion of monthly pregnancy testing and provide counseling on EFT risk to patients who can become pregnant were removed.

In addition, Travere proposed the following changes to the pharmacy requirements:

- Updated the outpatient pharmacy requirements to include counseling and verifying liver testing prior to initial dispense and every 3 months thereafter.
- [redacted] dispensed amount from 30-days' to 90-days' supply [redacted] outpatient pharmacies to allow for greater flexibility and align with changes to liver testing verification and counseling cadence, per proposed updates to the label.
- [redacted] a "one-time" override authorization to dispense a greater than 90-days' supply (previously 30- days' supply) by certified outpatient pharmacies, if authorized by the certified prescriber.
- Include an exception for pharmacies (inpatient and outpatient), from [redacted] to "Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers."

Reviewer Comment: *We agree with the proposed changes related to removal of EFT risk as it aligns with changes to the REMS Document and the RMNL issued on March 11, 2025. Edits regarding timing of counseling and verification of liver testing requirements for outpatient pharmacies align with those for HCPs and patients and align with the proposed updates in labeling. The addition of the exception language for dispensers reinforces that only certified pharmacies can distribute, transfer, loan, or sell Filspari. We agree with allowing outpatient pharmacies to dispense up to a 90-days' supply to allow greater flexibility and to align the dispense with the changes in liver testing and counseling cadence.*

However, we do not agree with [redacted] *. Additionally, we do not agree with* [redacted]

(b) (4)

(b) (4) *These concerns were discussed with the Division of Cardiology and Nephropathy (DCN), and they concurred with our recommendation.*[a]

The Applicant will need to revise the inpatient and outpatient pharmacy requirements as follows:

- *Allow dispense of 90-days' supply for outpatient pharmacies.*
- *Maintain dispense of 30-days' supply for inpatient pharmacies.*
- *Maintain* (b) (4) *"one-time" authorization to dispense a greater than 90-days' supply and document the reason for a "one-time" override must be reported to the REMS.*

These proposed changes should be aligned in the outpatient and inpatient pharmacy enrollment forms.

These changes should also be reflected in the ***Prescriber and Pharmacy Guide****,* ***REMS website****, and REMS Supporting Document.*

3.2.2. REMS Applicant Requirements and Materials

3.2.2.1. Training

The **Prescriber and Pharmacy Guide** and the **Patient Guide** were updated to reflect the removal of EFT risk, change in liver testing, verification, and counseling cadence to every 3 months, (b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: *We agree with the removal of EFT risk and change in liver testing cadence in the* ***Prescriber and Pharmacy Guide*** *and* ***Patient Guide*** *as these changes align with the changes in the REMS Document and the March 11, 2025, RMNL. We also agreed with allowing outpatient pharmacies to dispense a 90-days' supply during treatment to align with the proposed liver testing and counseling cadence (every 3 months during treatment with Filspari).* (b) (4) (b) (4) *maintain inpatient pharmacy dispensing to a 30-days' supply and for outpatient pharmacies to maintain a "one-time" override authorization to dispense greater than 90-days' supply, if required.*

3.2.2.2. Operations

Travere proposed the following changes in the REMS website:

- Included a pop-up alert on the REMS website to alert participants on the removal of EFT risk in the REMS.
- Removed the REMS participant requirements related to the risk of EFT.
- Changed the liver testing cadence to every 3 months during treatment (previously every month for the first 12 months, then every 3 months during treatment).
- Updated timing of counseling and verification of liver testing requirements for outpatient pharmacies to align with that of the HCP and patient, and to align with proposed updates to the label.
- (b) (4)

[a] Email communication with DCN, dated June 2, 2025.

- (b) (4)
- Included a reminder message in the Outpatient Pharmacy Portal for the pharmacies to complete counseling on hepatotoxicity.
- Allowed Office Contacts to "start enrollment" for patients to assist HCPs with the administrative work of completing patient demographics.
- Added a REMS verification code expiration date after the REMS verification code is generated for the Outpatient Pharmacy Portal to improve compliance with outpatient pharmacy staff to use the REMS verification code within the timeframe before expiration date.
- Added date enrolled patient was last counseled on hepatotoxicity and date liver testing was last verified to the Outpatient Pharmacy Portal to assist pharmacy staff with complying with changes in requiring these activities prior to initial dispense and then every 3 months.
- Updated Outpatient Pharmacy and Inpatient Pharmacy requirements to "Not distribute, transfer, loan, or sell FILSPARI, except to certified dispensers."

Reviewer Comment: *DRM does not agree with* (b) (4) (b) (4) (b) (4) *Travere will need to update the* ***REMS website*** *(public and non-public) to reflect the changes as described in Section 3.2.1.3.*

3.3. REMS Assessment Timetable

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

4. Supporting Document

The REMS Supporting Document was changed to include the background of the REMS modification currently under review.

The REMS goal and objective was updated to align with the March 11, 2025, RMNL to remove the risk of EFT in the REMS. This resulted in removing EFT associated information from REMS participants requirements on:

a. assessing reproductive status of patients who can get pregnant,
b. monitoring pregnancy testing prior to initiation, during treatment, and 1 month after discontinuation of treatment, and
c. counseling on the risk of EFT and effective contraception.

Liver testing cadence was updated to every 3 months during treatment to align with the changes in the REMS Document and proposed labeling. Accordingly, the REMS participant requirements (HCPs, patients, and pharmacies) were updated to reflect these changes.

The outpatient and inpatient pharmacy requirements were updated to "Not distribute, transfer, loan, or sell Filspari, except to certified dispensers". The Applicant also proposed to (b) (4) (b) (4) Travere also proposed (b) (4) (b) (4) (b) (4).

Further, Travere removed key performance indicators (KPIs) associated with EFT risk. Lastly, the Applicant provided minor revisions, formatting changes, and updated version control throughout the REMS.

Reviewer Comment: *We find the proposed changes in the REMS goal and objective statements along with the proposed removal of EFT risk information, associated key risk messages for EFT risk, and changes in the liver testing cadence acceptable. The risk of EFT and actions to take in patients who can get pregnancy are included in the proposed labeling updates.*

As noted in section 3. Review of the Proposal REMS Modification, we agree to allow outpatient pharmacies to dispense a 90-days' supply to align with the proposed change to the liver testing cadence. (b) (4) (b) (4) *. Additionally, we do not agree with* (b) (4) (b) (4)

Additionally, the Agency developed key risk messages (KRMs) for REMS participants that align with the REMS goal and guide the risk messaging used throughout the REMS materials. These KRMs are to be included in the REMS Supporting Document (RSD) above the Key Performance Indicators (KPI) section.

4.1. REMS Assessment Plan

The Applicant proposed several changes to the Filspari REMS Assessment Plan including removing all metrics associated with the risk of EFT. In addition, the Applicant proposed an edit to metric 5.k., (b) (4)

Reviewer Comment: *The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) reviewed the Assessment Plan and found all of the Applicant's proposed revisions to the metrics associated with the risk of EFT to be acceptable.*

In addition to the changes proposed by Travere, the Agency determined that the Assessment Plan requires further revisions to ensure that the plan adequately informs REMS assessments. As mentioned in section 3.2.1.3 of this review, the Agency does not agree with (b) (4) (b) (4) *DMAMES did not agree with the Applicant's proposed edit to metric 5.k. and proposed an alternative revision for the Applicant. In addition, two new assessment categories were added to their proposed plan: Safe Use Behaviors (Liver Testing), and Health Outcomes (Hepatotoxicity). Metrics on Safe Use Behavior and Health Outcomes are needed to assess if the REMS requirements are being met and to evaluate the effectiveness of the REMS strategies in mitigating the risk. The Applicant will be provided with a redlined copy of the Assessment Plan that includes the changes summarized below.*

- *Age stratification was removed from metric 2 "REMS Utilization Data"*
- *Metric 5, "Filspari REMS Compliance", was revised by relocating 5.a.iii, and 5.h to the newly created assessment category, "Safe Use Behaviors" as metric 6, "Liver Testing."*
- *Metric 5.k. was revised* (b) (4) (b) (4)
- *A new metric, "Hepatotoxicity" was added, to evaluate available health outcomes data related to hepatotoxicity*

5. Discussion

Travere proposed to remove information associated with the risk of EFT (e.g., pregnancy testing, monitoring, verification of monthly pregnancy testing, counseling on EFT risk and effective contraception options) to align with the RMNL issued on March 11, 2025. Travere removed the **Change in Reproductive Status Form** as a REMS material as this form is no longer necessary with the removal of the EFT risk. The proposed labeling updates will inform HCPs that Filspari is contraindicated in pregnancy, to counsel patients who can get pregnant on the potential risk to the fetus, and use effective contraception prior to initiating, during treatment, and for two weeks after treatment discontinuation.

Travere extended liver monitoring cadence to "every 3 months during treatment" to align with their proposed labeling. Travere also proposed to (b) (4) (b) (4) (b) (4). DRM and DCN do not agree with (b) (4) (b) (4) Further, Travere proposed to (b) (4) (b) (4) (b) (4). DRM and DCN do not agree with (b) (4) (b) (4) (b) (4) (b) (4) maintain a "one-time" authorization to dispense greater than 90-days' supply by outpatient pharmacies with documentation of the reason for the override.

Further enhancements to the REMS were added to:

a. Improve compliance by outpatient pharmacies with the addition of:
    i. a verification code expiration date.
    ii. reminder message in the Outpatient Pharmacy Portal for the pharmacies to complete counseling on hepatotoxicity, and date enrolled patient was last counseled on hepatotoxicity and date liver testing was last verified.
    iii. requirement for pharmacies to "Not distribute, transfer, loan, or sell Filspari, except to certified dispensers".
b. Allow Office Contacts to "start enrollment" for patients to assist HCPs with the administrative work of completing patient demographics.
c. Alert REMS participants on the removal of the EFT risk in the REMS.

Travere updated these changes throughout the REMS (REMS Document, RSD, and relevant REMS materials). Additionally, the Agency developed KRMS for the REMS participants that align with the REMS goal and guide the risk messaging used throughout REMS materials. These KRMs are to be included in the REMS Supporting Document (RSD).

The REMS Assessment Plan was revised by the Applicant to remove all metrics associated with the risk of EFT. The Applicant also proposed edits to metric 5.k., (b) (4) (b) (4) (b) (4) DMAMES requests additional revisions to the REMS assessment plan to reorganize and add metrics on Safe Use Behavior and Health Outcomes and/or Surrogates of Health Outcomes categories. These revisions are needed to inform REMS assessment as it relates to compliance with REMS requirements and the risk of hepatotoxicity.

6. Conclusions and Recommendations

DRM does not find the proposed REMS modification for Filspari (sparsentan) as submitted on October 28, 2024, and last amended on May 19, 2024, to be acceptable, as described in this review. Send the comments in Section 7 to Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 7 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on May 19, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comments:

1. We agree with the changes made to remove the risk of embryofetal toxicity throughout the REMS.
2. We do not agree with (b) (4) (b) (4) (b) (4). Make this change in all impacted REMS materials.
3. We do not agree with (b) (4) (b) (4) (b) (4). Maintain a "one-time" authorization to dispense a greater than 90-days' supply, if necessary. Documentation of the reason for a "one-time" override must be reported to the REMS. Correct this change in the relevant REMS materials (i.e., REMS Supporting Document).

REMS Document:

See General Comments above and align the recommended changes to the REMS Document. See redlined attached document.

REMS Materials:

1. Align the **Prescriber and Pharmacy Guide**, **Inpatient Pharmacy Enrollment Form**, and **REMS website** (public and non-public) with the recommended changes. See General Comments above and attached redlined documents.
2. The additional attached redlined documents (i.e., **Patient Enrollment Form**, **Prescriber Enrollment Form**, **Outpatient Pharmacy Enrollment Form**, and **Patient Guide**) include comments and edits to

improve clarity and readability of the REMS materials. We recommend ensuring that font and size of text is consistent throughout enrollment forms. Additionally, the names of REMS materials should be **bolded** without italics throughout each of the REMS materials, including mentions of REMS materials on the REMS website (e.g., "**Patient Enrollment Form**" should be used instead of "***Patient Enrollment Form"***).

REMS Supporting Document (RSD):

See General Comments above. Align the RSD with the information in the REMS Document and REMS materials.

Key Risk Messages

The Agency developed the following KRMS that align with the REMS goal and guide the risk messaging used throughout REMS materials. Include the following KRMs in the REMS Supporting Document (RSD) above the Key Performance Indicators (KPI) section.

KRMs for patients:

- There is a risk of liver problems.
- Get liver test before starting Filspari and every three months during treatment.

KRMs for prescribers:

- Hepatotoxicity can occur in patients taking Filspari.
- Perform liver testing before initiating treatment and every three months during treatment.
- Counsel the patient on the need for liver testing.

KRMs for pharmacies:

- Before initial dispense and every three months during treatment, verify that liver testing is complete.
- Counsel patients on the risk of hepatotoxicity before initial dispense and every three months during treatment.

Assessment Plan

The Agency requires revisions to the REMS Assessment Plan to ensure that the plan adequately informs REMS assessments. The changes are summarized below, and a redlined version is attached with additions underlined and deletions in ~~strikethrough~~.

a. Revise metric 2, "REMS Utilization Data," and remove the requirement to stratify by age.
b. Revise metric 5, "Filspari REMS Compliance," by relocating the crossed-out metrics (5.a.iii, and 5.h) to the newly created assessment category, "Safe Use Behaviors" as metric 6, "Liver Testing."
c. Revise metric 5.k. to capture the number of prescriptions for greater than 90-days' supply (outpatient) or greater than 30-days' supply (inpatient)
d. Include the new metric 8, "Hepatotoxicity," under the newly created "Health Outcomes and/or Surrogates of Health Outcomes" assessment category.

Submit a REMS amendment within 7 business days, by **COB July 22, 2025**, that addresses these comments.

Include the REMS Document, all appended materials, and the REMS Supporting Document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, all appended materials and supporting document.

The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	Tracked MS Word Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment Form	Tracked MS Word Clean MS Word, PDF version
4	Patient Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
5	Outpatient Pharmacy Enrollment Form	Clean MS Word, PDF version
6	Inpatient Pharmacy Enrollment Form	Clean MS Word, PDF version
7	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
10.	REMS Website	Tracked MS Word Clean MS Word, PDF version
Other Materials		
11	Proprietary REMS website (appendix to REMS Supporting document)	Tracked MS Word, Clean MS Word, PDF version
	Compiled REMS (consisting of REMS Document and REMS appended materials/ REMS website)	PDF

8. References

1. Wachter L. DCN. REMS Modification Notification Letter, dated March 11, 2025.

2. DeConti S. DCN. Safety Memorandum. Elimination (or Modification) of the Risk Evaluation and Mitigation Strategies (REMS) for products in the Endothelin Receptor Antagonist (ERA) pharmacologic class for embryofetal toxicity risk., dated February 28, 2025. .

9. Appendix

REMS Document

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Outpatient Pharmacy Enrollment Form

4. Inpatient Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

7. Prescriber and Pharmacy Guide

Patient:

10. Patient Guide

Pharmacy

12. Prescriber and Pharmacy Guide

40 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s005

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 216403 SUPPL # S-005 HFD #

Trade Name Filspari

Generic Name Sparsentan

Applicant Name Travere Therapeutics, Inc.

Approval Date, If Known August 27, 2025

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)/ SE-8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The changes supported by the clinical data includes:

1. Modification of the liver testing frequency in the product labeling (from monthly for 12 months, then every 3 months during treatment, to every 3 months during treatment).
2. Removal of the risk of embryo-fetal toxicity (EFT) from the Risk Evaluation and

Mitigation Strategy (REMS), and corresponding labeling changes.

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 216403 sparsentan

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

PROTECT Study - phase 3 trial, 021IGAN17001, entitled "A Randomized, Multicenter, Double-blind, Parallel-group, Active-control Study of the Efficacy
DUET Study - A randomized, double-blind, multicenter, phase 2 study in subjects ages 8 to 75 years with biopsy-verified primary FSGS
DUPLEX Study - Multicenter, international, phase 3, randomized, double-blind, active-controlled study of sparsentan in patients with FSGS

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1: **PROTECT Study**	YES ☒	NO ☐
Investigation #2: **DUET Study**	YES ☒	NO ☐
Investigation #3: **DUPLEX Study**	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:
Studies PROTECT, DUET and DUPLEX were all relied upon in NDA 216403 Original approval.

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1, #2, #3 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 137918 YES ☒ NO ☐

Explain:

Investigation #2& #3

IND (b) (4) YES ☒ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Anna Park
Title: Regulatory Project Manager
Date: September 19, 2025

Name of Deputy Division Director for Safety signing form: Selena DeConti, PharmD, MPH
Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

ANNA J PARK
09/19/2025 08:15:40 AM

SELENA D DECONTI
09/19/2025 08:21:31 AM

September 19, 2025

Needed to revise the studies in the form.

Please refer to the corrected review dated September 19th, 2025.

EXCLUSIVITY SUMMARY

NDA # 216403 SUPPL # S-005 HFD #

Trade Name Filspari

Generic Name Sparsentan

Applicant Name Travere Therapeutics, Inc.

Approval Date, If Known August 27, 2025

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)/ SE-8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The changes supported by the clinical data includes:

1. Modification of the liver testing frequency in the product labeling (from monthly for 12 months, then every 3 months during treatment, to every 3 months during treatment).
2. Removal of the risk of embryo-fetal toxicity (EFT) from the Risk Evaluation and

Mitigation Strategy (REMS), and corresponding labeling changes.

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 216403 sparsentan

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Maryam Changi for Anna Park
Title: Regulatory Project Manager
Date: August 28, 2025

Name of Deputy Division Director for Safety signing form: Selena DeConti, PharmD, MPH
Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

MARYAM CHANGI
08/28/2025 12:43:16 PM
on behalf of Anna Park

SELENA D DECONTI
08/28/2025 12:50:09 PM

From: Park, Anna
Sent: Tue 12 Aug 2025 06:29:04 PM -0400 UTC
To: 'Pradnya Bhagwat'; 'Lynley Thinnes'
Cc: 'Heidi Spanish'
Subject: NDA 216403 S.005 (sparsentan) - Information Request (Labeling) #5
Attachments: filspari-draft-med-guide-8.12.2025-redline (to firm).docx

Dear Pradnya,

Please find attached a draft copy of the Medication Guide with our revisions.

Also, please submit final labeling of the USPI to the NDA. This should reflect the final dates.

Kindly confirm receipt at your earliest convenience. We request a response by **noon on Friday, August 15, 2025**. You may submit a courtesy copy of your response by email followed by an official submission to your application

Thanks.
anna

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Phone: (301) 796-1129
Fax: (301) 796-9841

FDA U.S. FOOD & DRUG ADMINISTRATION

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/s/

ANNA J PARK
08/12/2025 06:41:11 PM
Please see Source Communication File, (.msg) for attachment

From: Park, Anna
Sent: Thu 07 Aug 2025 09:10:06 AM -0400 UTC
To: Pradnya Bhagwat; Lynley Thinnes
Cc: Heidi Spanish
Subject: NDA 216403 S.005 (sparsentan) - Information Request (Labeling) #4
Attachments: N216403s005 - Draft MG (To Firm 2025-08-06) (002).docx

Dear Pradnya,

Please find attached a draft copy of the Medication Guide with our revisions.

Kindly confirm receipt at your earliest convenience. We request a response by **noon on Monday, August 11, 2025**. You may submit a courtesy copy of your response by email followed by an official submission to your application

Thanks.
anna

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
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/s/

ANNA J PARK
08/07/2025 09:13:17 AM
Please see Source Communication File, (.msg) for attachment

Wachter, Lori

To: Pradnya Bhagwat
Subject: Filspari (sparsentan) NDA 216403 S-005
Attachments: 7.28.2025 revised rems-document-v14-20250424-clean.docx

Importance: High

Hi Pradnya,

In reference to the Filspari REMS modification currently under review (Supplement 005), we are providing an edit to the REMS Document under requirements for healthcare providers who prescribe. Line 9
(during treatment, every 3 months) should be revised to clarify that healthcare providers are required to counsel the patient on the risk of hepatotoxicity if they are not complying with the required liver testing. Please see attached redlined document.

Incorporate this change in the impacted REMS materials (REMS supporting document, **Prescriber Enrollment Form**, **Prescriber and Pharmacy Guide**, **and REMS website**) with your forthcoming August 1, 2025, REMS amendment submission.

Feel free to contact me with any questions.

Regards,

Lori

Lori Anne Wachter, RN, BSN, RAC-Drugs (US)
Regulatory Health Project Manager for Safety, Division of Cardiology and Nephrology
Center for Drug Evaluation and Research
Office of Cardiology, Hematology, Endocrinology and Nephrology
U.S. Food and Drug Administration
Tel: 301 796-3975
lori.wachter@fda.hhs.gov

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/s/

Lori A WACHTER
07/28/2025 02:22:48 PM

From: Park, Anna
Sent: Thu 17 Jul 2025 12:32:06 PM -0400 UTC
To: Pradnya Bhagwat; Lynley Thinnes
Cc: Heidi Spanish; Wachter, Lori
Subject: NDA 216403 S.005 (sparsentan) - Information Request (REMS) #3
Attachments: Filspari (Sparsentan) NDA 216403 REMS Assessment Plan_Redlined.docx, rems-document-v14-20250424-clean FDA Edits.docx, rems-inpatient-pharmacy-enroll-form-v14-20250424-FDA Edits.docx, rems-outpatient-pharmacy-enroll-form-v14-20250424-FDA Edits.docx, rems-patient-enroll-form-v17-20250424-clean FDA Edits.docx, rems-patient-guide-v14-20250424-clean FDA Edits.docx, rems-prescriber-enroll-form-v16-20250424-clean FDA Edits.docx, rems-prescriber-pharmacy-guide-v15-20250424-clean.docx

Dear Pradnya,

We have the following comments on the proposed REMS modification, submitted on May 19, 2025. Review of the REMS proposal is ongoing; these comments should not be considered final.

General Comments:

1. We agree with the changes made to remove the risk of embryofetal toxicity throughout the REMS.
2. We do not agree with (b) (4) (b) (4) (b) (4) Make this change in all impacted REMS materials.
3. We do not agree with (b) (4) (b) (4) (b) (4). Maintain a "one-time" authorization to dispense a greater than 90-days' supply, if necessary. Documentation of the reason for a "one-time" override must be reported to the REMS. Correct this change in the relevant REMS materials (i.e., REMS Supporting Document).

REMS Document:

See General Comments above and align the recommended changes to the REMS Document. See redlined attached document.

REMS Materials:

1. Align the **Prescriber and Pharmacy Guide**, **Inpatient Pharmacy Enrollment Form**, and **REMS website** (public and non-public) with the recommended changes. See General Comments above and attached redlined documents.
2. The additional attached redlined documents (i.e., **Patient Enrollment Form**, **Prescriber Enrollment Form**, **Outpatient Pharmacy Enrollment Form**, and **Patient Guide**) include comments and edits to improve clarity and readability of the REMS materials. We recommend ensuring that font and size of text is consistent throughout enrollment forms. Additionally, the names of REMS materials should be **bolded** without italics throughout each of the REMS materials, including mentions of REMS

materials on the REMS website (e.g., "**Patient Enrollment Form**" should be used instead of "***Patient Enrollment Form"***).

REMS Supporting Document (RSD):
See General Comments above. Align the RSD with the information in the REMS Document and REMS materials.

Key Risk Messages
The Agency developed the following KRMS that align with the REMS goal and guide the risk messaging used throughout REMS materials. Include the following KRMs in the REMS Supporting Document (RSD) above the Key Performance Indicators (KPI) section.
KRMs for patients:

- There is a risk of liver problems.
- Get liver test before starting Filspari and every three months during treatment.

KRMs for prescribers:

- Hepatotoxicity can occur in patients taking Filspari.
- Perform liver testing before initiating treatment and every three months during treatment.
- Counsel the patient on the need for liver testing.

KRMs for pharmacies:

- Before initial dispense and every three months during treatment, verify that liver testing is complete.
- Counsel patients on the risk of hepatotoxicity before initial dispense and every three months during treatment.

Assessment Plan
The Agency requires revisions to the REMS Assessment Plan to ensure that the plan adequately informs REMS assessments. The changes are summarized below, and a redlined version is attached with additions underlined and deletions in ~~strikethrough~~.

a. Revise metric 2, "REMS Utilization Data," and remove the requirement to stratify by age.
b. Revise metric 5, "Filspari REMS Compliance," by relocating the crossed-out metrics (5.a.iii, and 5.h) to the newly created assessment category, "Safe Use Behaviors" as metric 6, "Liver Testing."
c. Revise metric 5.k. to capture the number of prescriptions for greater than 90-days' supply (outpatient) or greater than 30-days' supply (inpatient)
d. Include the new metric 8, "Hepatotoxicity," under the newly created "Health Outcomes and/or Surrogates of Health Outcomes" assessment category.

Submit a REMS amendment within 7 business days, by **COB July 22, 2025**, that addresses these comments.

Include the REMS Document, all appended materials, and the REMS Supporting Document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, all appended materials and supporting document.

The next submission to the Gateway should include the following:

	Materials	Required Formats

1	REMS Document	Tracked MS Word Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment Form	Tracked MS Word Clean MS Word, PDF version
4	Patient Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
5	Outpatient Pharmacy Enrollment Form	Clean MS Word, PDF version
6	Inpatient Pharmacy Enrollment Form	Clean MS Word, PDF version
7	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
8	Patient Guide	Tracked MS Word, Clean MS Word, PDF version
10.	REMS Website	Tracked MS Word Clean MS Word, PDF version
Other Materials		
11	Proprietary REMS website (appendix to REMS Supporting document)	Tracked MS Word, Clean MS Word, PDF version
	Compiled REMS (consisting of REMS Document and REMS appended materials/ REMS website)	PDF

Kindly confirm receipt at your earliest convenience. We request a response by COB **on July 25, 2025**. You may submit a courtesy copy of your response by email followed by an official submission to your application.

Thanks.
Anna

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Phone: (301) 796-1129
Fax: (301) 796-9841

APPEARS THIS WAY ON ORIGINAL

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/s/

ANNA J PARK
07/17/2025 12:35:59 PM
Please see Source Communication File, (.msg) for attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:
CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Anna Park/OCHEN/DCN (301)796-1129

REQUEST DATE:
7/11/2025

NDA/BLA NO.:
216403 S.005

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Filspari (sparsentan)

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
8/28/2025

SPONSOR:
Travere Therapeutics, Inc.

PDUFA Date: **8/28/2025**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA216403\0137

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Apologies for the late notice. I thought I had placed a consult when the supplement came in.

Filing/Planning Meeting:

Mid-Cycle Meeting: 4/3/25

Labeling Meetings: 7/3/25

Wrap-Up Meeting: 7/17/25

SIGNATURE OF REQUESTER

Anna Park

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

ANNA J PARK
07/11/2025 01:52:53 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Anna Park/OCHEN/DCN/(301)796-1129

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
September 9, 2025		216403.S005	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Filspari (sparsentan)			**August 28, 2025**

NAME OF FIRM:	PDUFA Date: **August 28, 2025**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission: \\CDSESUB1\evsprod\NDA216403\0137

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Apologies for the late notice. Please review label. PI and med guide

Mid-Cycle Meeting: 4/3/25
Labeling Meetings: 7/3/25
Wrap-Up Meeting: 7/17/25

SIGNATURE OF REQUESTER Anna Park

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL X DARRTS

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/s/

ANNA J PARK
07/09/2025 08:00:32 AM

July 11th ,2025

This consult is no longer needed.

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:
CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Anna Park/OCHEN/DCN (301)796-1129

REQUEST DATE:
7/9/2025

NDA/BLA NO.:
216403 S.005

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Filspari (sparsentan)

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
8/28/2025

SPONSOR:
Travere Therapeutics, Inc.

PDUFA Date: **8/28/2025**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA216403\0137

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Apologies for the late notice. I thought I had placed a consult when the supplement came in.

Filing/Planning Meeting:

Mid-Cycle Meeting: 4/3/25

Labeling Meetings: 7/3/25

Wrap-Up Meeting: 7/17/25

SIGNATURE OF REQUESTER

Anna Park

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

ANNA J PARK
07/09/2025 08:02:18 AM

From: Park, Anna
Sent: Mon 30 Jun 2025 03:03:55 PM -0400 UTC
To: Lynley Thinnes
Subject: NDA 216403 S.005 (sparsentan) - Labeling Comments
Attachments: N216403s005 - Draft PI (To Firm 2025-06-30).docx

Dear Lynley,

I hope this email finds you well.

Please find attached our proposed draft of the USPI with our comments and recommendations.

Kindly confirm receipt at your earliest convenience. We request a response by **COB on Wednesday, July 9, 2025**. You may submit a courtesy copy of your response by email followed by an official submission to your application.

Thanks.
Anna

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Phone: (301) 796-1129
Fax: (301) 796-9841

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/s/

ANNA J PARK
06/30/2025 03:07:02 PM
Please see Source Communication File, (.msg) for attachments

Wachter, Lori

To: Lynley Thinnes
Cc: Pradnya Bhagwat
Subject: NDA 216403 -- Response Required by May 19, 2025

Importance: High

Hi Lynley,

Reference is made to your submission dated May 12, 2025, containing a Risk Evaluation and Mitigation Strategy (REMS) amendment for Supplement 5 (S-005), which requests (b) (4)

(b) (4)

We kindly request that you submit the revised REMS materials, reflecting the removal of the Elements to Assure Safe Use (ETASU) for embryo-fetal toxicity and reflecting the proposed change for the required liver monitoring every 3 months during treatment, as well as draft labeling to reflect these changes on or before May 19, 2025. This will allow for a comprehensive review of the information within the current review cycle.

Let me know if you have any questions.

Regards,

Lori

Lori Anne Wachter, RN, BSN, RAC-Drugs (US)
Regulatory Health Project Manager for Safety, Division of Cardiology and Nephrology
Center for Drug Evaluation and Research
Office of Cardiology, Hematology, Endocrinology and Nephrology
U.S. Food and Drug Administration
Tel: 301 796-3975
lori.wachter@fda.hhs.gov

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/s/

Lori A WACHTER
05/15/2025 01:44:14 PM

Bartlett, Silvia

From: Bartlett, Silvia
Sent: Friday, May 2, 2025 9:20 AM
To: Lynley Thinnes
Cc: Pradnya Bhagwat
Subject: NDA 216403 - Information Request #6

Dear Lynley Thinnes,
Please see below request for information regarding your supplement NDA 216403 application.

> Per DUET interim study report (Protocol RET-D-001) submitted as part of eCTD0009 you indicate that PK data will be collected for the DUET study. Specifically, you state that the "Pharmacokinetic (PK) results from the study are presented in a separate report." However, we were unable to locate the PK results report and the ADPC file associated with subject level data. Please submit this or provide justification as to why this information is not needed to support your clinical program.

Kindly confirm receipt of the IR and we request you provide a response by **COB May 05, 2025.**

Thanks,
Sarai

Silvia Sarai Bartlett, BS
Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Food and Drug Administration
silvia.bartlett@fda.hhs.gov
phone: (301) 796-7715
fax :(301) 796-9841

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/s/

SILVIA S BARTLETT
05/02/2025 02:23:21 PM

Bartlett, Silvia

From: Bartlett, Silvia
Sent: Wednesday, March 26, 2025 1:44 PM
To: Lynley.Thinnes@travere.com
Subject: NDA (b) (4) - Information Request

Dear Lynley Thinnes,
Please see below request for information regarding your supplement NDA 216403 application.

(b) (4)

Thanks,
Sarai

Silvia Sarai Bartlett, BS
Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Food and Drug Administration
silvia.bartlett@fda.hhs.gov

phone: (301) 796-7715
fax :(301) 796-9841

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/s/

SILVIA S BARTLETT
03/26/2025 02:26:08 PM

From: Park, Anna
To: Pradnya Bhagwat; Lynley Thinnes
Subject: NDA 216403 S.005 (sparsentan) - Information Request (clinical) #1
Date: Monday, March 3, 2025 11:08:00 AM
Attachments: image001.png

Dear Pradnya,

We have the following information request:

We request additional information and clarifications regarding your request to decrease the frequency of liver blood testing in the first 12 months of the REMS.

1. Please verify that all aminotransferase (AT) and bilirubin (TB) levels, including those from local or outside labs (hereafter "outside lab") were included in your rare glomerular disease (RGD) study pool, eDISH plots [Figure 1 of *your REMS Major Modification Data Package: Updated Exposure and Hepatotoxicity Data* dated Oct 21, 2024 (SN 0137, SDN 227)]. We noticed that PROTECT subject (b) (6) (Study 021IGAN17001) does not appear correctly plotted on your eDISH plots. This subject had AT and TB elevations that should put him above the 1 x ULN TB line in Temple's Corollary quadrant, yet there are no subjects with such abnormal TB levels in Temple's. We wonder if such plotting occurred because this subject's outside lab results were not in the lab dataset used to generate the eDISH plots, raising concerns that outside labs for other RGD subjects may have also been excluded. If all outside labs were included for the RGD eDISH plots, please clarify why subject (b) (6) is not above the 1 x ULN line. If outside labs were not included for all RGD subjects, please add them now, redo the eDISH plots, and comment on how adding the outside lab values affected your DILI case identification, whether by eDISH or other methods using peak on-treatment liver test values.

2. Please generate eDISH plots using all available peak AT and TB levels for post-market patients. Subjects who have not yet had their 1-month liver blood tests may be omitted.

3. Please confirm that the infrequency of liver blood tests done pre-, peri, and post-liver injury for post-market liver injury Case (b) (6) (Figure 23, page 117 of your *REMS Major Modification Data Package: Updated Exposure and Hepatotoxicity Data* dated Oct 21, 2024 (SN 0137, SDN 227)] corresponds to the non-compliance event for Prescriber (b) (6) [page 65, *REMS 24-Month Assessment Report* dated Feb 7, 2025 (SN 0140, SDN 240)]. If Case 2 (b) (6) and Prescriber (b) (6) are not related, comment on why liver blood tests for case (b) (6) were so infrequent and what remedial actions, if any, were taken.

Kindly confirm receipt at your earliest convenience. We request a response by **noon on March 17, 2025**. You may submit a courtesy copy of your response by email followed by an official submission to your application.

Thanks.
Anna

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Project Manager
Cardiology and Nephrology

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
Phone: (301) 796-1129
Fax: (301) 796-9841

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/s/

ANNA J PARK
03/03/2025 11:12:47 AM

NDA 216403/S-005

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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) received October 28, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Filspari (sparsentan) tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **August 28, 2025**.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

[1] Prescription Drug Labeling Resources website: https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] Pregnancy and Lactation Labeling Rule website: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights of Prescribing Information and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Other prescription drug labeling resources for the Prescribing Information, patient labeling, and carton and container labeling.

NATIONAL DRUG CODE(s)

Prior to the action date of your NDA we recommend you:

- Review the regulations that describe the requirements for national drug code (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].

- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.

- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website[3] or contacting eDRLS@fda.hhs.gov. Include the required additional data elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

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 the drug for this indication has orphan drug designation, you are exempt from this requirement.

[3] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/electronic-drug-registration-and-listing-system-edrls

If you have any questions, please contact Anna Park, Regulatory Project Manager, at Anna Park or anna.park@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

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/s/

MARY R SOUTHWORTH
12/26/2024 01:03:15 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DRISK **Mail: OSE**			FROM: DCN	
DATE 11/20/2024	IND NO.	NDA NO. 216403	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT 10/28/2024
NAME OF DRUG Filspari (sparsentan)	PRIORITY CONSIDERATION Still under review		CLASSIFICATION OF DRUG ERA	DESIRED COMPLETION DATE TBD

NAME OF FIRM: Travere Therapeutics

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- × OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Travere Pharmaceuticals submitted a supplement (S-005) that was determined to be an SE 8. There is clinical information submitted to change the frequency of the liver monitoring. A REMS modification was also submitted. Please review the REMS modification.

SIGNATURE OF REQUESTER Lori Anne Wachter RN, BSN, RAC – Drugs (US)	METHOD OF DELIVERY (Check all that apply) ×MAIL × DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

Lori A WACHTER
11/20/2024 01:37:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of New Drugs/Office of Inflammation and Immunity/ Division of Hepatology and Nutrition			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Anna Park/OCHEN/DCN/(301) 796-1129	
DATE 11/20/2024	IND NO.	NDA NO. 216403 S.005	TYPE OF DOCUMENT supplement	DATE OF DOCUMENT 10/28/2024
NAME OF DRUG sparsentan	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG dual endothelin angiotensin receptor antagonist (DEARA)	DESIRED COMPLETION DATE TBD

NAME OF FIRM: Travere Therapeutics

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Sparsentan (RE-021) is a that is a single molecule with antagonism of the endothelin type A receptor (ETAR) and the angiotensin II type 1 receptor (AT1R) approved for the treatment of IgA nephropathy (IgAN) (b) (4)

(b) (4)

On February 17, 2023, sparsentan received accelerated approval with a REMS for the risk of hepatotoxicity. A required postmarketing study was included as a condition of approval in order to characterize the liver safety profile of sparsentan. The final protocol for this postmarketing requirement (PMR), submitted on March 20, 2024, specifies a study size of at least 3000 patients and individual patient follow up for 2 years. On September 5, 2024, Sparsentan received full approval with the continued REMS for the risk of hepatotoxicity.

On July 19, 2024, a meeting was held with the Applicant to discuss the proposed modifications to the liver monitoring frequency in the REMS for the risk of hepatotoxicity for sparsentan. During the meeting, the Applicant presented the exposure data at the time of accelerated approval as well as the exposure data 1 year post-approval from a combination of the ongoing clinical trials (833 patient-years of exposure) and postmarket exposure (>2350

patient-years as of February 2024). The Applicant stated that in the last 5 months, the exposure had increased further by 400 patient-years to 2750 patient years overall, representing approximately 2800 patients. Based on the information provided during the meeting, the Agency indicated that it might be open to revisiting the frequency of monitoring (assuming the data support doing so) and recommended that the Applicant submit a Written Response Only (WRO) meeting request to ensure alignment on the data package that would be submitted prior to submitting the request for a modification.

On August 1, 2024, the Applicant submitted a request for a WRO meeting to reach alignment with the Division on the data package that would be submitted to support review of the proposed modifications to liver monitoring within the REMS for sparsentan. On September 19, 2024, the Division agreed that the proposed data package reflected the requests made at the July 19, 2024 meeting. The Division included additional recommendations to facilitate review of the data.

On October 28, 2024, the Applicant submitted a supplement proposing to change the liver testing frequency in the REMS from “monthly for 12 months, then every 3 months during treatment ” to “every 3 months during treatment.” **Please review the supplement and opine on the Applicant’s proposal.**

Of note, Skip Hayashi has previously provided input on this application.

Link to submission: \\CDSESUB1\evsprod\NDA216403\0137

SIGNATURE OF REQUESTOR Anna Park	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

ANNA J PARK
11/20/2024 11:14:34 AM

NDA 216403/S-005

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

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

Dear Lynley Thinnes:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 216403

SUPPLEMENT NUMBER: 005

PRODUCT NAME: Filspari (sparsentan) tablets

DATE OF SUBMISSION: October 28, 2024

DATE OF RECEIPT: October 28, 2024

This submission proposes the following major modification to the approved risk evaluation and mitigation strategy (REMS) for Filspari (sparsentan): liver testing frequency from “monthly for 12 months, then every 3 months during treatment” to “every 3 months during treatment” and corresponding labeling update. Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product made with this change. We have assigned the following supplement number to your submission, NDA Supplement 5 (S-005). Please use this supplement number for future submissions related to this/these proposed REMS modification(s).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 27, 2024, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

RESPONSIBILITIES UNDER TITLE VIII OF FDAAA AND 42 CFR PART 11

You are also responsible for complying with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) [42 U.S.C. § 282(j)], including its implementing regulations in 42 CFR part 11. Section 402(j) of the PHS Act was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Unless you have delegated your responsibilities to another entity, you are the "responsible party" and are required to submit registration and results information for each "applicable clinical trial" to the ClinicalTrials.gov data bank, as provided by section 402(j) of the PHS Act and 42 CFR part 11.

If you have questions, please call me at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

CDR Anna Park, MS, RPh, RAC
Senior Regulatory Health Project Management
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

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

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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.

/s/

ANNA J PARK
11/13/2024 11:12:04 AM