NDA 216403

ACCELERATED APPROVAL

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

Dear Ms. Thinnes:

Please refer to your new drug application (NDA) dated and received March 17, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Filspari (sparsentan) tablets.

We acknowledge receipt of your major amendment dated October 13, 2022, which extended the goal date by three months.

This NDA provides for the use of Filspari (sparsentan) tablets to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein to creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on a reduction of proteinuria. It has not been established whether Filspari slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the FDCA and 21 CFR 314.500, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

We acknowledge your January 23, 2023, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Filspari (sparsentan) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Results of ongoing stability should be submitted throughout the dating period as an amendment to your marketing application, as they become available, including the results of stability studies from the first three production lots.

ADVISORY COMMITTEE

Your application for Filspari was not referred to an FDA advisory committee because the application did not raise significant or controversial issues that would merit outside expertise or public discussion and due to concerns about the public release of information that could impact the integrity of the ongoing trial.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under accelerated approval pursuant to section 506(c) of the FDCA and 21 CFR 314.510 may require further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated February 9, 2023. This requirement, along with required completion dates, is listed below.

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[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.

4330-1 Conduct a randomized, double-blind, placebo-controlled trial to describe and verify the clinical benefit of sparsentan for the treatment of IgA nephropathy. The trial should be adequately powered and of sufficient duration to detect a treatment effect on the endpoint that will be used to describe and verify the clinical benefit.

The timetable you submitted on February 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	Completed
Final Protocol Submission:	Completed
Study/Trial Completion:	10/2023
Final Report Submission:	02/2024

Submit clinical protocols to your IND 137918 for this product.

You must submit status reports of the progress of each requirement to this NDA not later than 180 days after the date of approval of this drug and every 180 days thereafter (section 506(B)(a) of the FDCA as amended by section 3210(b) of the Food and Drug Omnibus Reform Act of 2022). The status report should include trial completion and final report submission dates, any changes in plans since the last report, and, for clinical trials, number of subjects entered into each trial (21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii)).

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hepatotoxicity and to identify an unexpected risk related to drug-drug interactions.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4330-2 Conduct a pharmacokinetic drug-drug interaction trial to evaluate the effect of sparsentan, once-daily, dosed to steady state on substrates for CYP2C9 and CYP2C19 in adult healthy volunteers

The timetable you submitted on February 9, 2023, states that you will conduct this study according to the following schedule

Draft Protocol Submission:	06/2023
Final Protocol Submission:	09/2023
Study Completion:	05/2024
Final Report Submission:	09/2024

4330-3 Conduct a pharmacokinetic drug-drug interaction trial to evaluate the effect of acid reducing agents on the exposure of sparsentan in adult healthy volunteers.

The timetable you submitted on February 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	09/2023
Study/Trial Completion:	05/2024
Final Report Submission:	09/2024

4330-4 Conduct a pharmacokinetic drug-drug interaction trial to evaluate the effect of sparsentan once-daily dosed to steady state on substrates for P-gp and BCRP in adult healthy volunteers.

The timetable you submitted on February 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	09/2023
Study Completion:	05/2024
Final Report Submission:	09/2024

4330-5 Conduct a prospective, single-arm safety study of patients exposed to sparsentan, with two years of follow-up to assess and characterize the risk of drug-induced liver injury (DILI). This study should analyze the clinical features of DILI cases with sparsentan, such as the injury's severity, type, latency, and specifically evaluate the incidence of Hy's law cases. Information for liver injury cases should be captured with structured follow up (e.g., monthly monitoring of serum liver tests) including dechallenge and rechallenge results. A hepatic adjudication committee (HAC) should assess both the severity of the liver injury and sparsentan's role in its development (i.e., causality). This study should aim to enroll enough patients such that if 0 events of Hy's law are observed, then the upper bound of the 95% confidence interval for the rate of Hy's law will be 1/1000.

The timetable you submitted on February 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	09/2023
Study Completion:	12/2027
Final Report Submission:	04/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 137918 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) include a requirement to report annually on the status of any required studies or clinical trials under section 505(o)(3).

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Filspari (sparsentan) to ensure the benefits of the drug outweigh the risks of embryo-fetal toxicity and hepatoxicity.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Filspari (sparsentan) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of embryo-fetal toxicity and hepatoxicity listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require: pharmacies that dispense the drug be specially

certified, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on March 17, 2022, amended and appended to this letter, is approved.

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

Your REMS must be fully operational before you introduce Filspari (sparsentan) into interstate commerce.

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

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

REMS Implementation and Operations

1. **Program Implementation (for the first assessment only)**
    a. Filspari REMS Launch Date
    b. Date when Filspari REMS materials became available on the REMS Website and via the Contact Center
    c. The dates stakeholders could enroll online, by mail, or by fax:
        i. Prescribers
        ii. Pharmacies
        iii. Patients
    d. Date when the Filspari REMS Website went live
2. **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) by patient type:
            1) Patients who can become pregnant
            2) Patients who cannot become pregnant
    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)

3. **REMS Utilization Data**
   a. Number and percentage of unique patients who received Filspari, new and total, by patient type (i.e., patients who can or cannot become pregnant) grouped by the following age ranges (years):
      i. <10
      ii. 10 - < 18
      iii. 18 - < 25
      iv. 25 - < 45
      v. 45 - < 53
      vi. 53+
   b. Number and percentage of prescriptions (first-fills and refills) dispensed for patients who can become pregnant and patients who cannot become pregnant stratified by:
      i. Healthcare Provider Specialty
      ii. Patient age as outlined in 3a above
4. **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
5. **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

6. **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
iii. Compliance with pregnancy and liver testing
    1. Number and percentage of all patients who can become pregnant who have documentation of a negative pregnancy test on the ***Patient Enrollment Form*** prior to treatment initiation.
    2. Number and percentage of all dispenses for patients who can become pregnant associated with confirmation from a certified pharmacy that monthly pregnancy testing was performed, or the prescriber authorized the refill prior to each dispense.
    3. 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.

4. If established thresholds for metrics 1-3 are not met, a root cause analysis of why each threshold was not met, and a proposed plan for specific measures or modifications to the REMS to meet the established threshold(s).

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 monthly patient pregnancy tests, liver tests, and monthly counseling)
g. Number and percentage of pharmacies by type (i.e., inpatient, outpatient) that did not provide verification of the authorized representative every two years
h. Number of one-time authorizations by prescribers (i.e., prescriber used clinical judgement and allowed the dispense without pregnancy and/or liver testing)
    i. Number and percentage authorized for missing pregnancy testing verification
    ii. Number and percentage authorized for missing liver testing verification
i. The number of certified prescribers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action
j. 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 either missed pregnancy testing or 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
k. Number of prescriptions dispensed of greater than 30-days' supply 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

l. Unintended system interruptions and corrective actions taken
m. Other barriers or delays in product dispensing and corrective actions taken
n. 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

7. Reproductive Potential Status Changes

Both in a flowchart and in the report narrative, report the following regarding the ***Change in Reproductive Potential Status Forms*** including:

a. Number of ***Change in Reproductive Potential Status Forms*** received, including the number of forms noted as a misclassification, error in classification, or correction to classification. Include the reasons these were classified as misclassifications or errors
b. Number of status changes to a patient who can become pregnant, including the rationale for the change as indicated on the ***Change in Reproductive Potential Status Form***. Also, report:
    i. Time between receipt of the ***Change in Reproductive Potential Status Form*** and confirmation that pregnancy testing occurred (time reported as a mean, median and standard deviation)
    ii. Verification that routine pregnancy tests of all patients who can become pregnant occurred prior to the next dispense following a change in status to a patient who can become pregnant
    iii. Number of times Filspari was dispensed prior to the patient getting their first pregnancy test following the status change to a patient who can become pregnant, any resulting adverse events, and corrective actions
c. Number of status changes to a patient who cannot become pregnant, including rationale for the change as indicated on the ***Change in Reproductive Potential Status Form***
d. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any patient by completing and submitting the ***Change in Reproductive Potential Status Form*** within ten (10) days of becoming aware of the change
e. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis

Health Outcomes and Surrogate of Health Outcomes

8. Pregnancy Cases

a. An analysis of all cases of pregnancy reported in association with Filspari from any source including but not limited to the following:
    i. The number of pregnancy exposures reported and stratified by source of exposure report (i.e., spontaneous report, reported via the REMS, etc.)

b. Pregnancy incidence rate (in person-years) to allow comparison with expected rates in the general population
c. A cumulative summary of both US and worldwide pregnancy cases should be provided and at a minimum, include the following information:
    i. Event identification number
    ii. Indication for Filspari
    iii. Contraceptive methods used
    iv. Outcome for each pregnancy
    v. Age of patient
d. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
e. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis

Knowledge

9. Evaluation of Knowledge of the Filspari REMS and Risks of Filspari (starting with the 12-month assessment then annually)

a. An evaluation of certified prescribers' knowledge of:
    i. the risk of embryo-fetal toxicity associated with Filspari
    ii. the risk of hepatotoxicity associated with Filspari
    iii. the need to confirm that patients who can become pregnant have a negative pregnancy test before treatment initiation
    iv. the need to confirm that patients have a liver test before treatment initiation
    v. the need for patients who can become pregnant to test monthly for pregnancy during treatment and for one month after discontinuing treatment
    vi. the need for patients to have a liver test monthly during treatment for the first 12 months, then every three months during treatment
    vii. the need to counsel patients about:
        - the risks
        - use of effective contraception for patients who can become pregnant
        - the need for a pregnancy testing monthly and for one month after discontinuing treatment for patients who can become pregnant and liver testing monthly for the first 12 months, then every three months during treatment
b. An evaluation of certified inpatient and outpatient authorized representatives' and trained pharmacists' knowledge of:
    i. the risk of embryo-fetal toxicity associated with Filspari
    ii. the risk of hepatotoxicity associated with Filspari
    iii. the need to confirm monthly that the patient's reproductive status has not changed prior to dispensing Filspari

iv. the need to confirm that patients who can become pregnant have a pregnancy test before treatment initiation
v. The need to confirm that patients have a liver test before treatment initiation
vi. the need to confirm that patients who can become pregnant test monthly for pregnancy during treatment prior to dispensing Filspari and for one month after discontinuing treatment
vii. the need to confirm that patients have liver testing monthly for the first 12 months, then every three months during treatment prior to dispensing Filspari
viii. the need to confirm that patients are counseled about the following prior to dispensing Filspari:
- the risks
- use of effective contraception for patients who can become pregnant
- the need for a pregnancy testing monthly and for one month after discontinuing treatment for patients who can become pregnant and liver testing monthly for the first 12 months, then every three months during treatment

c. An evaluation of enrolled patients' knowledge of:
i. the risk of serious birth defects
ii. the risk of liver problems
iii. The need for patients who can become pregnant to have a negative pregnancy test before starting Filspari
iv. The need for patients to have a liver test before starting Filspari
v. The need for monthly pregnancy testing for patients who can become pregnant before each refill and for one month after discontinuing treatment
vi. The need for monthly liver testing for the first 12 months, then every three months during treatment
vii. The need to use effective contraception and avoid pregnancy for patients who can become pregnant

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches,

study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan **and** non-compliance plan **and** root cause analysis plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocols for the knowledge surveys for FDA review within 90 days of this letter.

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)**

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[4]

REPORTING REQUIREMENTS

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

REQUESTED PHARMACOVIGILANCE

We request that for a period of 5 years, you submit serious cases of hepatotoxicity reported with Filspari (sparsentan) tablets. Conduct structured follow up of these cases to capture liver specific and related information and have them reviewed by a hepatic adjudication committee. Submit all cases of hepatotoxicity from your global safety database and the published medical literature as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)). For each case, provide case-level patient identifiers to reliably distinguish these cases from those in the observational study conducted under PMR 4330-5. If available, provide reporter information to facilitate the collection of follow-up information. Provide comprehensive summaries and analyses of cases of hepatotoxicity reported from clinical studies and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Filspari (sparsentan) tablets, as well as relative to prior periodic safety reports.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could

[4] https://www.fda.gov/media/128163/download.

benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Anna Park, Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- 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/

LISA B YANOFF
02/17/2023 01:49:52 PM