CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM) and 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)

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Review Completion Date	February 17, 2023
Subject	Evaluation of Need for a REMS
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics
Therapeutic Class	Endothelin and angiotensin receptor antagonist
Formulation(s)	200 mg and 400 mg oral film-coat tablet
Dosing Regimen	200 mg once daily for 14 days then increase to 400 mg once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Filspari (sparsentan) is necessary to ensure the benefits outweigh its risks. Travere Therapeutics (Travere) submitted a New Drug Application (NDA) 216403 for Filspari (sparsentan) under an accelerated approval pathway with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. The serious risks associated with sparsentan are embryo-fetal toxicity and hepatotoxicity. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

Filspari appeared efficacious in its primary outcome of the relative change from baseline in urine protein-to-creatine ratio (UPCR) at Week 36 in patients with persistent overt proteinuria and at high risk of disease progression. In the pivotal study, PROTECT, the UPCR change at Week 36 was statistically significant at 35% lower for the sparsentan arm compared to the irbesartan arm. However, DRM and the Division of Cardiology and Nephrology (DCN) agree that a REMS is necessary to ensure that the benefits outweigh the risks of hepatotoxicity and embryofetal toxicity. DCN recommends accelerated approval of Filspari, with a REMS, for the indication to reduce proteinuria in adults with primary IgAN at risk for rapid disease progression.

Renin-angiotensin blockers such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and endothelium receptor antagonists (ERAs) are known to be associated with embryofetal toxicity. Hepatotoxicity is also associated with ERAs (bosentan, ambrisentan, and macitentan) but the severity differs depending on the specific drug product. Approved ERA products have a REMS to mitigate the risk of embryo-fetal toxicity, and some also require a REMS to mitigate the risk of hepatotoxicity. Evidence that sparsentan can cause potential fetal harm was identified in animal reproductive studies, and drug induced liver injury (DILI) signals were observed in the clinical development program. Considering limitations of available data associated with accelerated approval and the known risks of hepatotoxicity and embryo-fetal toxicity associated with the ERA drug-class, DRM and the Division of Cardiology and Nephrology (DCN) determined that labeling will not be sufficient to mitigate these risks.

Travere initially proposed a REMS to mitigate only the risk of embryo-fetal toxicity, but during the application review, evidence of potential hepatotoxicity was identified in the clinical development program and the risk of hepatotoxicity was added to the Filspari REMS. Travere's proposed REMS to mitigate the risk of hepatotoxicity and embryo-fetal toxicity is similar to the ERA REMS (i.e. Bosentan REMS and Ambrisentan REMS) approved for pulmonary artery hypertension (PAH).

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

Objectives:

1. Monitor for elevations in liver enzymes in patients exposed to FILSPARI

2. Ensure that patients who can become pregnant are not pregnant before initiating FILSPARI
3. Minimize exposure in patients who may become pregnant while taking FILSPARI

The Filspari REMS includes the following REMS elements: ETASU A (healthcare providers who prescribe Filspari are specially certified), ETASU B (pharmacies that dispense Filspari are specially certified), ETASU D (dispensing of Filspari may be done only with the documentation of safe-use conditions), and ETASU E (each patient using Filspari is subject to certain monitoring), an implementation system, and a timetable for submission of assessments. Prescribers must certify and attest to complying with the requirements of the REMS. Patients must be enrolled to ensure they are aware of the risks and monitoring requirements. Pharmacies must certify to ensure awareness of the risks and attest to complying with the requirements of the REMS, by establishing processes and procedures to verify that prescribers are certified, patients are enrolled, safe use conditions such as monthly counseling on the risks is provided to the patient, verifying the patient completes required testing before each dispense, and verifying the patient's reproductive status has not changed.

In addition to a REMS, the Applicant will be required to perform enhanced pharmacovigilance and will be required to conduct a postmarket study to further characterize the hepatotoxicity risk. The risk of hepatotoxicity and embryo-fetal toxicity will also be communicated in labeling as a boxed warning (BW) and these risks will also be included in the warnings and precautions. Labeling will also include a contraindication (CI) for pregnancy. Dependent upon assessment findings and postmarket requirements results, FDA may modify the REMS or consider other regulatory actions.

1. Introduction

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Filspari (sparsentan) is necessary to ensure the benefits outweigh its risks. Travere Therapeutics (Travere) submitted a New Drug Application (NDA) 216403 for Filspari (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This application is under review in the Division of Cardiology and Nephrology (DCN) under an accelerated approval program. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of sparsentan outweigh the risks of hepatotoxicity and embryofetal toxicity.

2. Background

2.1. Product Information

Filspari (sparsentan), a new molecular entity[a], is an angiotensin II (AT_1R) and endothelin (ET_AR)receptor antagonist proposed for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

and older. Both endothelin-1 (ET-1) and angiotensin II (Ang II) are vasoactive peptides that exert renal hemodynamic actions and promote cell growth, oxidative stress, and increased expression and activity of proinflammatory and profibrotic mediators associated with several kidney diseases, including IgAN. Sparsentan, with its inhibitory effect on receptor function, is thought to reduce proteinuria and slow progression of kidney disease associated with IgAN.

Sparsentan is proposed to be available as 200 mg and 400 mg oral film-coated tablets. The proposed dosing regimen is 200 mg once daily orally for 14 days and increased to 400 mg daily thereafter, as tolerated.[b]

Sparsentan obtained an Orphan Designation for the treatment of IgAN in the United States (US) on January 11, 2021. The Applicant submitted Filspari NDA 216403 for IgAN under an accelerated approval program. Sparsentan is not currently approved in any jurisdiction. Travere is also developing sparsentan for focal segmental glomerulosclerosis (FSGS), another rare kidney disease, under IND (b) (4).

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216403 relevant to this review:

- 12/4/2020: A Type C meeting was held to discuss the clinical development of sparsentan under IND 137918/ NDA 216403 for IgAN and IND (b) (4) for FSGS. The Agency informed the Applicant that there is a risk of embryo-fetal toxicity with sparsentan, and other approved endothelin receptor antagonists (ERAs) are approved with a REMS. The Agency informed the Applicant that at this time, we do not have sufficient information to determine whether a REMS will be necessary and if necessary, what the required REMS elements will be. The Agency asked that the Applicant provide a proposal to mitigate the potential risk of embryo-fetal toxicity for FDA to review.
- 1/11/2021: Sparsentan granted Orphan Drug Designation for the treatment of IgAN in the US.
- 5/14/2021: In the Type B Pre-NDA meeting for sparsentan under (b) (4) for FSGS, the Agency informed the Applicant that a REMS will likely be necessary to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity.
- 3/20/2022: NDA 216403 submitted for the treatment of IgAN in adults aged 18 years and older.
- 5/11/2022: Filing Communication Letter issued to inform the Applicant that there were no identified filing issues, and the application was granted priority review status. However, the Applicant was informed the proposed Sparsentan REMS was incomplete as only the PDF versions were submitted, whereas, both MS Word and PDF versions of the REMS are needed for review.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 5/17/2022: The Agency issued an information request (IR) to the Applicant to request a submission of both MS word and PDF versions of the proposed Sparsentan REMS for review.
- 6/9/2022: The Applicant submitted an amendment to the application with the MS word and pdf versions of the proposed REMS (eCTD sequence no. 19).
- 6/28/2022: A Mid-cycle meeting (MCM) was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that we agreed a REMS is necessary to mitigate the risk of embryo-fetal toxicity. We also informed the Applicant that an imbalance in hepatotoxicity events is under review and the Applicant should review how other ERAs mitigate this risk.
- 9/1/2022: The Agency sent the Late Cycle Meeting (LCM) background package to the Applicant which informed the Applicant additional REMS requirements are necessary to mitigate the risk of hepatoxicity.
- 9/12/2022: The Agency held a LCM teleconference with the Applicant. The Agency re-affirmed the necessity of a REMS to mitigate the risk of hepatotoxicity and directed the Applicant to submit an amendment to the proposed REMS.
- 9/23/2023: The Agency provided interim comments (IC1) to the Applicant in response to their REMS submission, dated March 20 and June 9, 2022.
- 10/13/2022: Travere submitted a REMS amendment to NDA 216403 to amend their REMS proposal to include the risk of hepatotoxicity, in addition to embryo-fetal toxicity. Travere proposed requiring liver testing every (b) (4) (eCTD sequence no. 42).
- 10/21/2022: The Agency issued a Review Extension for Major Amendment letter to Travere in response to the REMS amendment submitted to NDA 216403 on October 13, 2022, extending the PDUFA goal date to February 17, 2023.
- 11/14/2022: The Agency responded via email to Travere on the necessity for monthly liver testing instead of every (b) (4) liver testing, as proposed by Travere.
- 11/22/2022: Travere responded via email to the Agency's November 14, 2022 comments to require monthly liver testing in the Filspari REMS. In their response, Travere (b) (4) proposed monthly liver monitoring for the first year, and quarterly thereafter. Travere asserts that by the end of the first year (after approval), there will be sufficient data from the clinical trials available to further characterize the hepatotoxicity risk.
- 12/13/2022: The Agency sent interim comments (IC2) to the Applicant in response to their REMS amendment, dated October 13, 2022. In IC2, the Agency agreed to the Applicant's proposed timeframe for liver testing as communicated in the November 22, 2022 correspondence.
- 12/19/2022: Travere submitted a REMS amendment to NDA 216403 in response to the Agency's IC2, dated December 12, 2022 (eCTD sequence no.44).

- 1/18/2023: The Agency sent interim comments (IC3) to the Applicant in response to their REMS amendment, dated December 19, 2022.
- 1/19/2023: The Agency sent via email further information requests to the Applicant.
- 1/27/2023: Travere submitted a REMS amendment in response to the Agency's IC3 and IR from January 18 and 19, 2023 (eCTD sequence no. 48).
- 1/30/2023: The Agency sent interim comments on the proposed Assessment Plan.
- 2/3/2023: The Agency sent interim Comments (IC4) to the Applicant in response to their REMS amendment, dated January 27, 2023.
- 2/9/2023: A teleconference was held with Travere to confirm alignment of the REMS submission.
- 2/9/2022: Travere submitted a REMS amendment in response to the Agency's January 30, 2023 and February 3, 2023 ICs (eCTD sequence no.53).
- 2/10/2023: The Agency sent Interim Comments (IC5) to the Applicant in response to their REMS amendment, dated February 10, 2023.
- 2/13/2023: Travere submitted a REMS amendment in response to the Agency's IC5 from February 10, 2023 (eCTD sequence no.55).

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

IgAN, also known as Berger's disease, is a rare, progressive kidney disease in which up to 40% of subjects progress to end-stage kidney disease (ESKD) within 10 to 20 years following diagnosis.[1c] It is the most common cause of primary glomerulonephritis worldwide with the greatest frequency in East Asians and Caucasians.[2] IgAN is diagnosed by kidney biopsy and is characterized by the finding of immune deposits, predominantly containing polymeric immunoglobulin A (IgA), in the glomerular mesangium of the kidney resulting in damage to the glomerular filtration barrier, proteinuria, hematuria, and decreased glomerular filtration rate.[1]

IgAN is estimated to affect approximately 169,000 individuals in the US.[d] IgAN can occur at any age, but clinical onset is most common during the third decade of life.[1,3] Thus, most patients are diagnosed in their 20s or 30s and face the prospect of dialysis or the need for kidney transplantation. There is approximately a 2:1 male-to-female predominance in North American and Western European populations in both adults and children. Currently in the United States (US), there are 13,825 IgAN

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] OOPD. Prevalence estimates for IgAN in 2010, email communication dated December 7, 2021.

patients who have reached ESKD (median age of 52 years).[4e] Once renal replacement therapy (RRT) is initiated, the risk of premature death increases considerably. The expected remaining life span for dialysis patients 50 to 54 years of age is 8 years for men and 7.7 years for women. ESKD patients have high mortality with the mortality rate being 2.5-fold higher than that of cancer patients (USRDS 2020).[5] There is high recurrence of IgAN (as much as 50% to 60% in patients) following kidney transplantation and the estimated 10-year incidence of graft loss due to disease recurrence is approximately 10%.[6]

3.2. Description of Current Treatment Options

The standard of care (SOC) for the management of IgAN involves off-label use of renin-angiotensin aldosterone system (RAAS) inhibitors such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) along with lifestyle modifications such as dietary sodium and protein restriction, smoking cessation, weight control, and exercise, as appropriate, to decrease proteinuria and control blood pressure.[7] However, even with optimization of these therapies, overt proteinuria (> 0.75g/d -1g/d) remains along with continued loss of renal function and progression to ESKD in many patients with up to an average annual loss of eGFR of 7ml/min/1.73 m.[1,2] Both ACEI and ARB drug products have a well-established risk for embryo-fetal toxicity, which is prominently addressed in labeling as a box warning (BW) and listed as a risk in warnings and precautions (W&Ps), along with a contraindication for pregnancy.

Tarpeyo, (a delayed-release capsule formulation of budesonide), NDA 215935, a glucocorticoid, received approval in US on December 2021 to reduce proteinuria in adults with IgAN who are at high risk of disease progression (those with urine protein-to-creatinine ratio or UP/C > 1.5 g/g).[8] Tarpeyo was approved under an accelerated approval program based on a reduction in proteinuria; a confirmatory study for Tarpeyo is on-going. Treatment with Tarpeyo is associated with adverse reactions of systemic glucocorticoids such as hypercortisolism and adrenal axis suppression, immunosuppression, hypertension, diabetes, peripheral and facial edema, acne, weight gain, and hirsutism which may be contraindicated or not considered appropriate for some patients with IgAN. Another potential therapy, Farxiga (dapagliflozin), NDA 202293, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, was approved in April 2021 to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.[9] Farxiga may have an increasing role in the treatment of IgAN. As very limited therapies are available specifically for the management of IgAN, there remains a high unmet medical need for IgAN patients with persistent proteinuria >1 g/day, as they remain at high risk for progression to ESKD and premature death.

While Sparsentan has ERA activity, currently approved ERAs have not been used to manage patients with IgAN. ERA products currently approved for the treatment of pulmonary arterial hypertension (PAH) include, bosentan, ambrisentan and macitentan and are approved with a REMS to mitigate embryo-fetal toxicity. Bosentan and ambrisentan were also approved with a REMS to mitigate the risk of hepatotoxicity. However, the risk of hepatotoxicity was removed from the REMS and labeling for

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

ambrisentan due to postmarketing data that showed ambrisentan's hepatotoxicity rates were similar to background hepatotoxicity rates. The hepatotoxicity risk remains for bosentan as fatal hepatic events were observed in the clinical development program and in postmarketing. In addition to a REMS, FDA-approved labeling for all three ERA agents includes a boxed warning (BW) and warnings and precaution for embryo-fetal toxicity and a contraindication for pregnancy; bosentan also has an additional boxed warning for hepatotoxicity. Both bosentan and macitentan contain a Warning and Precaution for hepatotoxicity.

4. Benefit Assessment

To support the accelerated approval of Filspari, the Applicant submitted results of an interim analysis of a Phase 3 study, 021IGAN17001 (PROTECT; NCT03762850). PROTECT is an ongoing 114-week, randomized, double-blind parallel-group, active-controlled, multicenter, global study with an open-label extension (OLE) period of up to 156 weeks (for a total of up to 270 weeks) in subjects with IgAN who have persistent overt proteinuria (≥ 1 g/day) and remain at high risk of disease progression despite being on a stable dose (or doses) of an ACEI and/or ARB. In PROTECT, subjects were randomized 1:1 into 2 treatment arms (141 in the sparsentan arm and 140 subjects in the irbesartan arm). Sparsentan subjects were initiated on 200 mg once daily for 14 days then increased to 400 mg once daily, whereas subjects in the irbesartan arm received 150 mg once daily for 14 days followed by 300 mg once daily. The mean age was 46 years (range 18 to 76 years); 69% were male, 62% White, 35% Asian, and 1% Black or African American. Baseline clinical characteristics for eGFR and proteinuria were comparable between treatment groups. The percentage of subjects with hematuria at baseline was 56%.

Interim analysis of the PROTECT study demonstrated that it met its primary endpoint of the relative change from baseline in urine protein-to-creatine ratio (UPCR) at Week 36 for accelerated approval. The ratio of the geometric mean ratio of UPCR at 36 weeks relative to baseline was 35% lower (95% CI: 23% to 45% lower) for the sparsentan arm compared to the irbesartan arm ($p<0.0001$).[f] Efficacy findings were consistent across key subgroups, including key demographic and baseline disease characteristics. The confirmatory endpoint to verify clinical benefit will evaluate the rate of change of eGFR over a 110 week period (eGFR total slope at 2 years). Key secondary endpoints for the interim analysis are considered exploratory as the study is ongoing and include rate of change in eGFR chronic slope at 1 year and 1-year eGFR total slope. Confirmatory secondary endpoints include eGFR chronic slope at 2 years, and the rate of change in eGRF over 2 years (eGFR total slope at 2 years). Overall, the analyses on 1-year and 2-year eGFR slopes based on available observed data favor the sparsentan arm.

The clinical reviewers concluded that the submitted data provide substantial evidence of sparsentan's effectiveness in reducing proteinuria, a reasonably likely surrogate for a treatment's effect on kidney failure in patients with IgAN who are at high risk of disease progression. The clinical reviewer also concluded that the size of the treatment effect on proteinuria seen in the interim analysis in the PROTECT study is reasonably likely to predict clinical benefit and provide confidence that the second

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

phase of the trial is adequately powered to detect treatment effect on the endpoint that will be used to describe and verify the clinical benefit.

5. Risk Assessment & Safe-Use Conditions

The pivotal Phase 3 study, PROTECT, comprises the major source of safety data for sparsentan in the treatment of IgAN. Additional data on the hepatotoxicity risk of sparsentan include the ongoing Phase 2 study, RET-D-001 (DUET; NCT01613118) and the Phase 3 study, 021FSGS16010 (DUPLEX; NCT03493685) in FSGS subjects. The safety population includes 404 patients enrolled in PROTECT who received at least one dose of study treatment during the interim analysis period. The mean and median exposure duration was balanced between the sparsentan and the irbesartan groups. No deaths were reported during the interim data period. Serious adverse events (SAEs) and severe adverse events were balanced between the two treatment groups. More patients in the sparsentan group (7.9%) experienced treatment emergent adverse events (TEAEs) leading to permanent discontinuation of study drug than in the irbesartan group (4.5%). Adverse events of special interest (AESIs) for sparsentan versus irbesartan, respectively, included fluid retention mostly related to peripheral edema (12% versus 6%), hypotension including dizziness (24% versus 10%), acute kidney injury (4% versus 1.5%), hyperkalemia (11% versus 9%), tachycardia (1.5% versus 1%), and anemia (6% versus 3%). Imbalances observed in these AESIs are consistent and expected due to sparsentan's mechanism of action and will be included in Filspari's labeling as warnings and precautions (5.4 Hypotension, 5.5 (b) (4), 5.6 Hyperkalemia, and 5.7 Fluid retention).[g] This is consistent with other labeling for ERAs and ARB drug products and the clinical reviewer considers labeling will be adequate to manage these AESIs.

Due to its activity as an ERA, the risks of embryo-fetal toxicity and hepatoxicity are of interest with Sparsentan. As previously mentioned, bosentan, ambrisentan, and macitentan are all approved with a REMS to mitigate the risk of embryo-fetal toxicity, and the bosentan REMS also includes hepatoxicity as a serious risk. Hepatotoxicity and embryo-fetal toxicity risks for sparsentan are further described below.

5.1. Hepatotoxicity

The clinical reviewers identified potential drug induced liver injury (DILI) with sparsentan in the clinical development program for rare chronic kidney disease (CKD) which includes both the IgAN and FSGS population.[10] There were no identified Hy's Law cases (although there was a "near miss" case as sparsentan was discontinued before the total bilirubin reached Hy's Law level), and no cases of jaundice. However, an imbalance of Temple's Corollary at elevated aminotransferase (AT) > 5 times upper limit of normal (ULN) consistent with potential for increased hepatocellular injury was observed in subjects treated with sparsentan. The Division of Hepatology and Nutrition (DHN) identified 5 cases (four probable and one possible) of potential DILI in the PROTECT trial for IgAN and 1 probable case in the

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

DUPLEX trial for FSGS; three of the four probable DILI cases in PROTECT had positive rechallenges (elevations of liver enzymes when sparsentan was re-initiated) with hepatocellular injuries which were mostly modest and resolved when sparsentan was held. DHN noted two major challenges in assessing the DILI risk with sparsentan: (1) the number of patients with chronic kidney disease exposed to sparsentan in the clinical development program was small (500 patients), and well below the desired threshold of a few thousand patients which provides a 95% chance of detecting a 1 in 1000 risk of a Hy's Law case, and (2) latency from drug initiation to the event of DILI was unusually long for the probable and possible cases (mean 200 days, range 28-406 days). The DHN reviewer concluded that DILI is a potential risk of sparsentan and the potential for Hy's Law events may occur with greater exposure in the postmarket population. DHN recommends monthly monitoring of liver tests, for at least 12 to 14 months, to mitigate the risk of hepatotoxicity and allow for intervention, such as withholding sparsentan, to prevent further liver injury, if sparsentan is approved.

5.2. Embryo-fetal Toxicity

Both ERA and RAAS drug classes (which includes ACEIs and ARBs) are known to be teratogenic through different mechanisms of action. ET-1 is crucial to early embryonal development whereas ACEI/ARBs are associated with impaired fetal development in the second and third trimesters. Sparsentan shares a mechanism of action with both classes of drugs (ET-1 antagonist and ARB) and is expected to have teratogenic effects.[11] No human data is available on embryo-fetal toxicity for sparsentan. Anomalies in fetal development and decreased postnatal survival were observed in sparsentan animal studies. Dose-dependent toxicity of craniofacial malformations, skeletal abnormalities, embryo-fetal lethality, and reduced fetal weight were observed at doses of 80, 160, and 240 mg/kg/day in pregnant rats administered sparsentan. The area under the curve (AUC) at the lowest dose tested (80 mg/kg/day) was approximately 10 times the AUC at the maximum recommended human dose (MRHD) of 400 mg/day. In the sparsentan clinical development program, there were 5 pregnancies in 4 patients during the interim analysis period (1 experienced spontaneous abortion after discontinuation of treatment with sparsentan and become pregnant again within 2 months, one pregnancy of a partner in the sparsentan treatment group; 1 patient in the irbesartan group experienced spontaneous abortion 6 weeks after discontinuation of treatment, another patient in the irbesartan group became pregnant after 10 months on study medication and had an elective abortion). All study treatments were discontinued when pregnancy was detected. No congenital anomalies have been reported thus far following any pregnancy during the study.

Based on data from animal reproduction studies and the known embryo-fetal toxicity associated with the mechanism of action of sparsentan, the review team concluded that sparsentan can cause fetal harm when administered to pregnant patients and will be contraindicated during pregnancy. As noted earlier all ERA products approved for PAH have a REMS to mitigate the risk of embryo-fetal toxicity. Travere proposes in their application submission that sparsentan not be initiated in patients who can become pregnant unless the result of a pretreatment pregnancy test is negative and effective contraception is practiced. Filspari labeling will consist of a BW, warnings and precautions for embryo-fetal toxicity, and a contraindication for pregnancy. In addition, Travere proposed a REMS to mitigate the risk of embryo-fetal toxicity with elements to ensure safe use (ETASU) consisting of prescriber

certification (ETASU A), pharmacy certification (ETASU B), documentation of safe use conditions (ETASU D), each patient using the drug is subject to certain monitoring (ETASU E), an implementation system, and a timeline for required assessments.

6. Expected Postmarket Use

6.1. Healthcare Setting

Filspari is intended to be dispensed from a specialty pharmacy for chronic daily oral administration by the patient in an outpatient setting but may also be utilized in an inpatient setting. The prescribing population for Filspari is primarily nephrologists. These prescribers may not be aware of the risk of hepatotoxicity with sparsentan and the need for liver monitoring as this is a new drug class for treating IgAN. However, nephrologists are likely familiar with monitoring requirements for Jynarque (tolvapan), NDA 204441, approved in 2018 for autosomal dominant polycystic kidney disease (ADPKD) with a REMS to mitigate the risk of serious and potentially fatal liver injury. The Jynarque REMS requires prescribers to monitor liver enzymes in patients at specific intervals during treatment and to report liver test results to the REMS.

Nephrologists should be familiar with the risk for embryo-fetal toxicity as this risk is well established in the SOC pharmacotherapies (such as ACEI and ARBS) used to reduce proteinuria in patients with CKD including IgAN. However, there is uncertainty as to whether these prescribers are familiar with the need for routine monthly pregnancy testing with Filspari as this is not necessary for patients on ACEI and ARBs. Healthcare providers who prescribe and pharmacies that dispense Filspari will need to understand the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari and actions to take to mitigate these risks.

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

Travere proposed a REMS to mitigate the risk of embryo-fetal toxicity, as this is a known risk in ERA and ARB drug classes.[12] The proposed REMS is similar to REMS approved in the ERA drug class to mitigate the risk of embryo-fetal toxicity. The Applicant did not propose a REMS to mitigate the risk of hepatotoxicity in their initial submission. During the review of this application, the review team determined sparsentan has DILI potential and a REMS would be necessary to mitigate this risk. Imbalances in hepatic safety signals were observed in the clinical development program and the ERA drug class are known to have this risk with varying severity depending on the specific drug product.

The final Filspari REMS consists of ETASU that include prescriber certification (A), pharmacy certification (B), documentations of safe use conditions (D), each patient using the drug is subject to certain monitoring (E), an implementation system, and a timetable for submission of assessments of the REMS. Below is an overview of the Applicant's proposed REMS as submitted on March 20, 2022 and amended to include the changes made during the review of the application.

7.1.1. REMS Goals

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

Reviewer's Comments: *DRM agrees with the proposed goals and objectives of the REMS. Travere's initially proposed goal for the Filspari REMS as submitted on March 20, 2022 is as follows:*

(b) (4)

[redacted]

As noted earlier, during the course of the review, the review team determined the REMS for Filspari must also mitigate the risk of hepatotoxicity, in addition to embryo-fetal toxicity, due to potential DILI signals observed in the clinical development program. Travere submitted a REMS amendment to include the risk of hepatotoxicity on December 19, 2022.

When determining the goals for the Filspari REMS, DRM evaluated the risks, potential care gaps, prior experiences with similar drug classes, the drug use process, and how the goals of the REMS align with the public health prevention aims. DRM identified potential care gaps such as stakeholders (prescribers, patients, and pharmacists) may not be aware of the actions needed to ensure safe use, as this is a new drug class for the management of IgAN. Based on our evaluation, the overarching goal of the Filspari REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity and reflects the serious risks listed in the BW of the proposed labeling for Filspari. All stakeholders will need to be aware and take actions to mitigate these risks. Actions such as documenting a negative pregnancy test in patients who can become pregnant before initiation of treatment aligns with primary prevention (as defined by the World Health Organization [WHO]), to prevent exposure to Filspari, if pregnant. Monitoring for

elevations in liver enzymes and for pregnancy status during treatment aligns with secondary prevention to mitigate adverse events with early detection and prevent worsening outcomes. To achieve the goal of mitigating the risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari, the REMS will ensure: 1) prescribers, pharmacists, and patients are educated on these risks, 2) prescribers and pharmacists counsel patients on these risks, 3) prescribers assess for elevations in liver enzymes and pregnancy status before and during treatment, and 4) pharmacists verify safe use conditions (counseling, completion of required tests, reproductive status has not changed, patient is enrolled in the REMS, and the prescriber is certified) are met prior to dispensing.

Travere updated the REMS goal based on the Agency's ICs from September 23, 2023, December 13, 2022, and January 18, 2023. Travere also updated the REMS goal to align with the order of the risks presented in the proposed Filspari labeling (with hepatotoxicity listed before embryo-fetal toxicity). (b) (4)

7.1.2. REMS Elements

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification (A) pharmacy certification (B), documentation of safe use conditions (D), and each patient using the drug is subject to certain monitoring (E).

ETASU A: Prescriber Certification

The Applicant proposed that a prescriber must certify in the Filspari REMS prior to prescribing. To become certified, prescribers must review the prescribing information (PI) and the ***Prescriber and Pharmacy Guide***. The prescriber must complete and submit the ***Prescriber Enrollment Form*** to the REMS.

On the ***Prescriber Enrollment Form***, prescribers agree to do the following:

Prior to initiating treatment with Filspari, the prescriber must, for all patients, counsel on the risk of hepatotoxicity, assess liver test results, and assess the patient's reproductive status. For patients who can become pregnant, the prescriber must counsel on the risk of embryo-fetal toxicity and assess pregnancy status. The prescriber must enroll all patients in the Filspari REMS by a submitting a completed ***Patient Enrollment Form*** to the REMS. The prescriber must document the patient's reproductive status, affirmation of liver test assessment and negative pregnancy status (for patients who can become pregnant) on the ***Patient Enrollment Form*** that is submitted to the REMS.

During treatment, the prescriber must assess the patient's liver test results monthly for the first 12 months, then every 3 months during treatment, and pregnancy status monthly (for patients who can become pregnant). The prescriber must counsel the patient on the risk of hepatotoxicity and embryo-fetal toxicity if they are not complying with the required monthly pregnancy testing or if they are not using effective contraception (for patients who can become pregnant).

After treatment discontinuation and for 1 month afterwards, the prescriber must assess the patient's pregnancy status for patients who can become pregnant.

The prescriber must report a change or misclassification in reproductive status at all times to the REMS. However, the Applicant did not include a requirement for a prescriber to report annual verification of reproductive status for pre-pubertal females similar to other ERA REMS.

Reviewer's Comments: *We agree with the requirement for prescriber certification. The prescriber certification requirement in the Filspari REMS is similar to the prescriber certification requirement in the ERA REMS approved for PAH. Although prescribers, mainly nephrologists, are familiar with the risk of embryo-fetal toxicity associated with ACEI and ARBs commonly used in the CKD population to manage proteinuria, product labeling for ACEI and ARBs do not require prescribers to perform monthly pregnancy testing. In addition, prescribers may not be as aware of the hepatotoxicity risk associated with Filspari. As Filspari is a new drug class for this indication and prescribers may not be familiar with its risks, having prescribers certify in the REMS will ensure that prescribers are educated on the risks and will help ensure safe use conditions are met prior to prescribing (i.e., patients are counselled, enrolled, and monitored before and during treatment with Filspari) which supports the goal and objectives of the REMS. We agree with not requiring prescribers to annually verify the reproductive status of pre-pubertal patients as Filspari is indicated for adults only. The need for pre-pubertal annual verification of reproductive status may be reassessed if postmarketing use indicates significant use in pre-pubertal patients. If at any time a prescriber becomes aware of a change or misclassification in reproductive status, the REMS includes a requirement to report this change to the REMS.*

ETASU B Pharmacy Certification:

The Applicant proposes that Filspari be dispensed only by certified pharmacies. Pharmacies must become certified by naming an authorized representative who will coordinate REMS activities on behalf of the pharmacy, review training materials, enroll in the REMS, and ensure all relevant staff are trained in the REMS to obtain a REMS verification code from the REMS and document safe use conditions such as confirming completion of liver and pregnancy testing, counseling on the risks of hepatotoxicity and embryo-fetal toxicity, and the patient's reproductive status has not changed before each dispense per the processes and procedures developed by the pharmacy. To maintain pharmacy certification, if the authorized representative changes, the new authorized representative must re-certify in the REMS.

The REMS includes different requirements for inpatient and outpatient pharmacy dispensing. Before dispensing, the outpatient pharmacy obtains a REMS verification code from the REMS by contacting the REMS to verify the patient is enrolled and the prescriber is certified in the REMS. In addition, the pharmacy must document and submit that safe use conditions have been met before dispensing Filspari through the processes and procedures established as a requirement of the REMS, to include confirmation of counseling on hepatotoxicity and embryo-fetal toxicity (for patients who can become pregnant), patient's reproductive status has not changed, completion of liver testing (monthly for the first 12 months and every 3 months during treatment) and pregnancy testing (before initial dispense and monthly during treatment for patients who can become pregnant) or the prescriber authorizes refill if required testing is not completed. The pharmacy must not dispense more than a 30-days' supply.

The REMS requirements for the inpatient pharmacy are the same as the outpatient pharmacy except that inpatient pharmacy must obtain a REMS verification code from the REMS by contacting the REMS to verify a patient is enrolled in the REMS and is under the care of a certified prescriber or attest to completing patient enrollment prior to discharge. The inpatient pharmacy must also document and verify confirmation of counseling on hepatotoxicity and embryo-fetal toxicity (for patients who can become pregnant), patient's reproductive status has not changed, completion of liver testing (monthly for the first 12 months and every 3 months during treatment) and pregnancy testing (before initial dispense and monthly during treatment for patients who can become pregnant) through the processes and procedures established as a requirement of the REMS.

Review Comments: *We agree with the requirement for pharmacy certification. The pharmacy certification requirements are similar to other ERA REMS, such as in the Ambrisentan and Bosentan REMS. Outpatient pharmacies are required to obtain a REMS verification code, which verifies prescriber certification and patient enrollment. This verification only partially verifies two out of the five safe use conditions of the REMS, whereas the dispensing authorization obtained from the REMS for Bosentan and Macitentan REMS verifies all safe use conditions. To complete verification of all safe use conditions, the pharmacist must also document and submit verification of counseling, patient's reproductive status has not changed, and confirmation of required liver and pregnancy test completion, as applicable, to the REMS prior to dispensing. This process of verifying safe use conditions is acceptable as other REMS with similar risks fulfill the verification of safe use conditions differently. Outpatient pharmacies must submit daily dispensing data to the REMS that includes confirmation of all[h] REMS requirements for safe use to ensure compliance with the safe use conditions. Inpatient pharmacies maintain records of their dispensing and safe use requirements. The records are subject to auditing by the REMS to ensure compliance with the safe use requirements. Due to the nature of the inpatient setting, greater flexibility for patient access to Filspari is provided. The inpatient pharmacy may dispense Filspari to patients provided the patient is enrolled and under the care of a certified prescriber, or will be enrolled prior to discharge.*

Although the Filspari REMS is similar to other ERA REMS for PAH, there are several differences in the pharmacy requirements. Travere initially proposed (b) (4) *. In addition, Travere proposed outpatient pharmacies to dispense 30-days' supply* (b) (4) *. The review team discussed these differences between the proposed Filspari REMS and other ERA REMS and concluded that the pharmacy requirements in the Filspari REMS should align with the ERA REMS.* (b) (4) *. The pharmacist will document and submit completion of pregnancy testing in patients who can become pregnant to the REMS and will continue to confirm that the patient's reproductive*

[h] *All REMS requirements for safe use consists of prescriber certification and patient enrollment, and pharmacy confirmation consisting of documentation of counseling, test completion, and verification of reproductive status*

status has not changed as one of the safe use conditions for dispensing through the processes and procedures established as a requirement of the REMS. We agree with allowing for both inpatient and outpatient pharmacies to dispense 30-days' supply as this will not impact the safe use of Filspari. However, we do not agree with [redacted] (b) (4) *. Limiting dispensing to a 30-days' supply upon each refill will support monthly pregnancy testing is completed as there is potential for pregnancy to occur if monthly pregnancy testing is missed* [redacted] (b) (4) *. This approach is similar to the ERA REMS. DRM communicated this change to Travere in our December 13, 2022 IC and Travere accepted this change.*

ETASU D: Documentation of Safe Use Conditions

The Applicant proposed to include patient enrollment in the Filspari REMS to ensure that patients have been counseled by their prescriber on the drug's risks, understand the monitoring requirements, and the need to use effective contraceptives (for patients who can become pregnant), and how to recognize signs and symptoms of hepatotoxicity. In addition, pharmacies must confirm counseling, completion of required testing, and confirm patient's reproductive status has not changed prior to dispensing. The pharmacy also checks that the prescriber is certified, and the patient is enrolled in the REMS. These requirements are documented and verified by the pharmacy and submitted to the REMS through processes and procedures established by the certified pharmacy as a requirement of the REMS.

Reviewer Comments: *We agree with the requirement of documentation of safe use conditions. The proposed safe use conditions are similar to other ERAs approved for PAH with similar risks. During the course of the review, DRM recommended that liver and pregnancy tests result dates be included in the* ***Patient Enrollment Form*** *to assess time lapse between patient enrollment and initiation of therapy. However, the Applicant noted testing dates are not required in other REMS with similar risks within the patient enrollment forms, and the proposed labeling did not require testing dates to be included. DRM agreed that in lieu of having the testing date included in the* ***Patient Enrollment Form****, information be added to the training materials and pharmacy portal to educate and prompt pharmacists to confirm that the liver and pregnancy tests were performed since the last refill and to ensure all safe use conditions are met in addition to obtaining a REMS verification code. In addition, we recommended changing the* [redacted] (b) (4) *to be contacted by the REMS if pregnancy occurs to a statement of understanding, as this is more appropriate statement* [redacted] (b) (4) *. These changes were communicated to the Applicant on February 3, 2023 and the Applicant accepted them and these changes were incorporated in the February 10, 2023 REMS amendment.*

ETASU E: Monitoring

The Applicant proposed to include liver testing prior to initiation and during treatment monthly for the first 12 months, then every 3 months thereafter, and pregnancy testing at initiation, monthly, and one month after discontinuation of treatment as described in the prescribing information. Prescribers are to order and assess the required tests, and the pharmacy is to confirm required testing has been completed and submit documentation to the REMS.

Reviewer Comments: *We agree with the necessity of liver and pregnancy testing to ensure safe use conditions for patients who are prescribed Filspari.* (b) (4) *.*[15] (b) (4) *given the limited data available, the number of probable cases of DILI, a "near-missed" Hy's Law case, positive rechallenges, prolonged latency in development of DILI, the small population size exposed to sparsentan, and concerns that prescribers may not be familiar with the risk and need for close monitoring of hepatotoxicity with sparsentan for the IgAN population,* (b) (4) *frequent liver monitoring is required to ensure the benefits outweigh the risk of hepatotoxicity in patients who are administered Filspari.*[17] *This was communicated to the Applicant in our ICs on November 14, 2022. The Applicant countered with a proposal for monthly liver monitoring for the first year and every three months, thereafter in their November 22, 2022 REMS amendment. The review team agreed with the Applicant's liver monitoring proposal. Though the monthly liver monitoring frequency for the first year would be slightly below the observed maximum latency period to detect onset of DILI observed in the clinical trial, it would likely capture most of the cases of DILI and allow time for the completion of the phase 3 studies in the CKD program.*[18] *The Agency will also require a PMR to further characterize the risk of hepatoxicity, and indicated the inclusion of hepatotoxicity as a serious risk in the REMS could be re-evaluated pending the outcome of further studies. The Applicant submitted a REMS amendment on December 19, 2022 to update liver monitoring requirements and to incorporate the changes provided in the Agency's ICs dated December 12, 2022.*[19] *The monitoring frequency language for hepatotoxicity in the REMS was updated to monitor monthly for the first 12 months then every 3 months during treatment to align with the language in the proposed labeling in the February 3, 2023 REMS amendment.*[20]

The frequency of pregnancy testing is acceptable and aligns with other ERA REMS with risk for embryo-fetal toxicity to prevent exposure prior to initiating Filspari and minimize potential exposure during and after treatment.

7.1.3. Implementation System

To support REMS operations, the Applicant proposes to maintain a REMS Call Center (RCC) and REMS website to support prescriber and pharmacy stakeholder's ability to interface with the REMS, to enroll and complete certification, and for prescribers to submit a change in the reproductive potential status of a patient. REMS materials will be made available by the Applicant through the website and call center. The Applicant will notify stakeholders of successful enrollment in the REMS within 1 business day and will update the database and notify certified pharmacies of a patient's change in reproductive status within one business day after receipt of a ***Change in Reproductive Potential Status Form***. The Applicant will ensure Filspari is only distributed to certified pharmacies by wholesalers who are compliant with the REMS requirements. The Applicant will establish and maintain a validated, secure database of all REMS participants who are enrolled and certified in the REMS and will ensure REMS participants access to the database to confirm prescriber and pharmacy certification and patient enrollment. The Applicant will ensure outpatient pharmacies provide daily dispense data documenting that counseling was completed and the appropriate liver and pregnancy testing, as applicable, was completed prior to each dispense to

the REMS. The Applicant will use data from certified pharmacies to identify patients who experience a shipment delay due to reporting a missed pregnancy test and/or liver test and reconcile product distribution data received daily against the list of enrolled patients in the REMS database. To ensure compliance with the REMS, the Applicant will verify the contact information of the certified pharmacy's authorized representative every 2 years, maintain adequate records to demonstrate that REMS requirements have been met, and establish audit and noncompliance plans.

Reviewer's Comments: *We agree with the Applicant's proposal to include an implementation system and provided comments on September 23, 2022 and December 13, 2022. The proposed implementation system aligns with other ERA REMS. The Applicant provided adequate detail in the REMS Supporting Document on how often the REMS reconciles the daily dispensing data from the outpatient pharmacy, operational hours of the RCC, and how confirmation of liver and pregnancy testing, and monthly counseling are captured in the REMS*

7.1.4. Timetable for Submission of Assessments

Travere must submit REMS Assessments at 12 months and annually from the date of the initial REMS approval.

Reviewer's Comments: *The Applicant initially proposed including a* (b) (4) *assessment, however, DMAMES and DRM have aligned to require Filspari REMS assessments to be submitted beginning at 12 months post-approval, then annually thereafter. Based on past experience with other approved REMS, assessment results at* (b) (4) *from approval have historically provided minimal data to assess and insufficient time for the Applicant to incorporate any recommendations made by the Agency between the* (b) (4) *and 12-month assessment reports. In addition, the Agency will be monitoring adverse event reports through an enhanced pharmacovigilance plan as they are submitted to the FDA Adverse Event Reporting System (FAERS).*

7.1.5. REMS Materials & Key Risk Messages

The Applicant included the following materials as part of the REMS submission:

- Prescriber Enrollment Form (previously: Prescriber Enrollment (b) (4) Form): serves to enroll prescribers in the REMS and for prescribers to attest they understand the requirements of the REMS as part of the process to become certified to prescribe Filspari.
- Patient Enrollment Form (previously: Patient Enrollment (b) (4) Form): completed by the prescriber and the patient to enroll the patient into the REMS and requires patients to attest they understand the risks of Filspari as well as the safe use and monitoring requirements of the REMS and for prescribers to attest on having assessed pregnancy and liver test results prior to initiating treatment.
- Outpatient Pharmacy Enrollment Form: completed by the outpatient pharmacy's authorized representative on behalf of the pharmacy to enroll and certify into the REMS. The outpatient pharmacy authorized representative attests they understand the requirements of the REMS as

part of the process to become certified to dispense and will train staff on the REMS requirements.

- Inpatient Pharmacy Enrollment Form: completed by the inpatient pharmacy's authorized representative on behalf of the pharmacy to enroll and certify in the REMS. The inpatient pharmacy authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense and will train staff on the REMS requirements.
- Prescriber and Pharmacy Guide: serves to inform prescribers and pharmacy staff of the serious risks associated with Filspari, the REMS requirements, and the responsibilities of the prescriber and pharmacies.
- Patient Guide (Previously (b) (4)): serves to inform patients on the serious risks associated with Filspari as well as the REMS Program and its requirements.
- Change in Reproductive Potential Status Form: completed by the prescriber to report a change or misclassification of the patient's reproductive potential status.
- REMS Website: serves as a source of information for stakeholders and part of the implementation system for the Applicant. It allows prescribers and pharmacies to enroll in the REMS online. Prescribers will be able to certify in the REMS by completing the Prescriber Enrollment form online. Prescribers will be able to enroll and manage patients online. Pharmacies will be able to certify in the REMS by completing the pharmacy enrollment form online. Upon certification of pharmacies, pharmacy staff will be able to verify prescriber certification and patient enrollment online. The REMS appended materials, including a link to the Prescribing Information and Medication Guide, will be available and able for download.

Reviewer's Comments: *We agree with the Applicant's proposed REMS materials, and communicated on December 12, 2022, January 18, 2023, January 19, 2023, and February 3, 2023, that changes needed to be made to the proposed materials. These changes included:*

- *Simplified nomenclature of REMS materials and alignment across the REMS*
- *Revised the statements in the* ***Patient Guide*** *and the* ***Patient Enrollment Form*** (b) (4) *to be contacted by the REMS if pregnancy occurs to a statement of understanding as this not a requirement reflected in the REMS Document.*
- *Aligned the REMS materials with the proposed labeling and Medication Guide*
- *Added further details in the REMS materials and website to ensure safe use conditions are met prior to dispensing (e.g., for pharmacy to verify completion of required testing prior to the first dispense and since last dispense and REMS website screenshots showing verification processes)*
- *Removed* (b) (4) *in the attestation statement from the* ***Inpatient Pharmacy Enrollment Form***

The Applicant will be providing certifications of translations for the ***Patient Enrollment Form*** *and* ***Patient Guide*** *within 30 days after the REMS approval as the Applicant intends to provide these materials in different languages (English, Spanish, and Chinese) and will submit them as a REMS correspondence.*

The Applicant did not include key risk messages with their submission of the REMS materials. See Section 8 of this review for DRM's proposed Key Risk Messages.

7.1.6. REMS Supporting Document

The REMS Supporting Document includes the background and the Applicant's rationale for the REMS currently under review. The Supporting Document also contains information on stakeholders' responsibility in the REMS, how they carry out those responsibilities, and how the REMS will be implemented. The Applicant appended the Wholesaler-Distributor Enrollment Form, REMS Assessment Plan (tabular format), and the post login screens to the Supporting Document.

Reviewer's Comments: *DRM requested additional information in the Supporting Document on September 23, 2022, December 13, 2022, January 18, 2023, January 19, 2023, February 3, 2023, February 10, 2023, and February 13, 2023, including updates to align sections of the Supporting Document with the REMS Document and REMS materials. Travere made all requested edits and provided further details on the stakeholder enrollment process, REMS verification process, and included post login screens showing the functionality of the REMS.*

The Applicant provided further details in the patient enrollment process such as how the REMS responds when incomplete enrollment forms are submitted, (e.g. missing required information such as prescribers not confirming assessment of liver test or negative pregnancy test result in the patient enrollment form) , how patients or guardians complete the enrollment process outside of the office visit, and that the enrollment process cannot be completed when the required data are not submitted or stakeholder signatures are missing on the enrollment forms.

The Applicant outlined verification processes that certified pharmacies (both outpatient and inpatient) must undertake to ensure safe use conditions are met with each dispense. The pharmacist must obtain from the REMS website portal or by contacting the REMS Coordinating Center by phone, a REMS verification code which verifies prescriber certification and patient enrollment in the REMS. Due to the nature of the inpatient setting and to not compromise drug access, the requirement for patients in the inpatient setting is that the patient must be enrolled and under the care of a certified prescriber or will be enrolled in the REMS prior to discharge. Therefore, the inpatient pharmacy may obtain a REMS verification code to dispense when: a) patient is not yet enrolled but the prescriber is certified (the REMS verification portal will include a reminder for the inpatient pharmacist that the patient must be enrolled prior to discharge), b) patient is enrolled and the prescriber is not certified (patient is under the care of a certified prescriber in the outpatient setting), and c) patient is enrolled and the prescriber is certified. The pharmacist must also verify and document completion of liver and pregnancy testing, counseling on risks, and confirm the patient's reproductive status has not changed with each dispense. These safe use requirements (obtaining a REMS verification code, confirmation of completion of liver and pregnancy testing, or prescriber authorizes override, counseling, and confirmation of patient's reproductive status has not changed) are submitted to the REMS. Dispensing authorization overrides may be granted for > 30-day supply or when testing is not confirmed if the prescriber provides a reason, and it is documented in the REMS. To confirm compliance with the safe use requirements, outpatient pharmacies must submit a daily dispensing report to the REMS, whereas the inpatient pharmacy develops its own processes and procedures to document safe use requirements and the REMS will monitor compliance via auditing.

The Applicant provided additional post login (non-public facing) website screenshots in the appendix to the REMS Supporting Document showing the functionalities of the prescriber and pharmacy portals. The prescriber portal allows for online patient enrollments, managing patients, and reporting changes to a patient's reproductive potential category. The prescriber portal also allows for assignment of "Office Contact Management" staff who serve on behalf of the prescriber to facilitate communication with the REMS. The "Office Contact Management" staff does not have any clinical or authoritative responsibilities to complete patient enrollment, submit a change in reproductive status, assess test results, or authorize refills. The pharmacy portal allows the pharmacist to obtain the REMS verification code as part of the confirmation of safe use conditions and overall authorization to dispense. Reminder messages are included in the pharmacy portal to alert pharmacy staff to ensure that all safe use conditions have been met in addition to obtaining a verification code. The Applicant provided further screenshots showing successful and unsuccessful scenarios for patient enrollment by prescriber and for successful and unsuccessful scenarios in obtaining REMS verification codes by the pharmacy.

7.1.7. REMS Assessment Plan

In order to meet the goal of the REMS to mitigate the risk of embryo-fetal toxicity, patients who can become pregnant are required to have a pregnancy test prior to initiation of therapy, and pregnancy tests are to be conducted monthly during treatment and for one month following treatment discontinuation. In addition, to mitigate the risk of hepatotoxicity, liver tests must be performed prior to initiation of therapy and monthly for the first 12 months, and then every 3 months during treatment. Assessment plan metrics are included to evaluate if the REMS is functioning as designed, to determine if stakeholders are compliant with REMS requirements, and to assess if the REMS is meeting its goal and objectives. Prescriber, pharmacist, and patient knowledge of the risks and required actions needed to mitigate the risks are assessed using knowledge surveys.

The following categories of metrics are included in the Assessment Plan: Program Implementation (for the first assessment only), certification and enrollment, utilization data, infrastructure and performance, audits, compliance, safe use behaviors, health outcomes and surrogate of health outcomes, and knowledge.

Travere submitted draft assessment plans on October 13, 2022 and December 19, 2022. DMAMES completed a review on January 30, 2023[i] and proposed revisions were sent to Travere on the same day. Final drafts of the assessment plan were submitted by the Travere on February 3, 2023 and February 7, 2023. Travere accepted the proposed revisions and inserted mostly editorial revisions to some of the metrics. The final assessment plan is included in Appendix 10.1.

Reviewer Comment:

- *There were three revisions to metrics of note made by Travere. For metrics that included, "* (b) (4) *" these were revised to "liver tests or testing." For compliance metric 6d,*

[i] The DMAMES review of the Filspari assessment plan can be accessed at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806ae082.

"[redacted] (b) (4)" was revised to "REMS dispensing verification code." For metrics that included the schedule of required liver testing, the following was revised: "[redacted] (b) (4) [redacted]" was revised to "monthly for the first 12 months, then every 3 months during treatment." These revisions were made to align with terminology in other REMS materials and labeling. DMAMES and DRM agree with these revisions to the assessment plan.

- *The REMS is designed to mitigate the risk of hepatotoxicity and embryo-fetal toxicity by ensuring that pharmacies verify that liver and pregnancy tests are performed when required prior to dispensing. The REMS does not require reporting of test results or collecting specific laboratory data. The REMS puts a structure in place to support prescribers to perform appropriate monitoring of patients. As designed, we assume that if testing is performed as required, the healthcare providers will assess the results for elevations in liver enzymes and pregnancy, and make adjustments to the patient's treatment as necessary per the training and Prescribing Information.*
- *Any reports of possible hepatotoxicity are to be reported as part of the Post-Marketing Requirements and through the required postmarketing reporting of adverse events including FAERS reports and Periodic Adverse Drug Experience Reports (PADER) per 21 CFR 314.80. The assessment plan does not include the reporting of safety surveillance data related to hepatotoxicity. The Division of Pharmacovigilance will be consulted with each assessment to provide a summary of events related to possible hepatotoxicity, and these data will be used as supportive information to further assess if the goal of the REMS is met.*

7.2. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on January 8, 2023, and completed a consult review on January 25, 2023, by Charuni Shah.[21] OPDP recommended to align the indication statement, language in training guides (Prescriber and Pharmacy Guide, and Patient Guide) and on REMS website with the fully approved indication from the PI, and the final approved Medication Guide (MG). Additionally, OPDP made recommendations to include further details on the risk of hepatotoxicity in the ***Prescriber and Pharmacy Guide*** and the ***Patient Guide***, a comprehensive list of symptoms of liver problems in the ***Patient Guide***, and a more accurate representation of severity of the risk of birth defects in the ***Patient Guide***. DRM accepted all the recommendations and provided them to the Applicant on February 3, 2023. The Applicant incorporated all edits in their February 10, 2023 REMS amendment.

7.3. Other Proposed Risk Management Activities

As this application is under an accelerated approval pathway, a postmarket study will be required to verify and describe the clinical benefit of Filspari. The Applicant did not propose additional risk management activities in their initial application submission.

Reviewer's Comments: *The review team identified potential for hepatotoxicity with Filspari and recommends an enhanced pharmacovigilance plan to expedite spontaneous liver injury case reports to the FDA and a postmarket requirement (PMR) of a single-arm observational safety study with 2 years of follow-up to further monitor and characterize this risk.*

We note that these other activities are outside of the scope of the REMS program and defer to Division of Pharmacovigilance and the Division of Epidemiology for review and input.

8. Discussion of Need for a REMS

Filspari appeared efficacious in its primary endpoint of the relative change from baseline in urine protein-to-creatine ratio (UPCR) at Week 36. DCN recommends accelerated approval of Filspari to reduce proteinuria in adults with primary IgAN at risk for rapid disease progression, generally a UPCR $\geq$ 1.5 g/g on the basis of the interim analysis of the efficacy and safety information currently available. IgAN is a rare serious kidney disease and an important cause of CKD and kidney failure. Only one product, Tarpeyo, NDA 215935, is approved in the US for the treatment of IgAN for patients at rapid risk of progression; it was approved under accelerated approval and a confirmatory study to verify efficacy is on-going. There is an unmet need for treatments that can slow the loss of kidney function in patients with IgAN at high risk for disease progression. The clinical reviewer concluded that given the currently available data on the efficacy and safety of the product and the intent of the Accelerated Approval Program, the indicated population should be limited to patients at risk of rapid disease progression over a relatively short time frame.

The serious risks associated with sparsentan under consideration for a REMS include embryo-fetal toxicity and hepatotoxicity. Embryo-fetal toxicity is a known risk for the ERA drug-class and products within this drug-class are approved with a REMS to mitigate this risk. Based on nonclinical data on reproduction, sparsentan can cause fetal harm when administered to pregnant women. To mitigate the risk of embryo-fetal toxicity in the clinical trial, pregnant subjects were excluded, and monthly pregnancy testing was conducted in patients who can become pregnant. During the course of the review, it was determined that the Applicant did not fully address the risk of hepatotoxicity. The review team identified imbalances in DILI signals and the DHN reviewer concluded that drug-induced liver injury is a potential risk of sparsentan. Though no Hy's law cases were identified in the clinical development program, the study population was small, and Hy's Law events may occur with greater exposure in the postmarketing population. DHN recommended monthly monitoring of liver testing, for at least 12 to 14 months, to mitigate the risk of hepatotoxicity if sparsentan is approved.

DRM identified potential care gaps such as stakeholders (prescribers, patients, and pharmacists) may not be aware of the actions needed to mitigate the risks of hepatotoxicity and embryo-fetal toxicity and to ensure safe use of Filspari, as this is a new drug class for the management of IgAN.

The review team conducted a comprehensive evaluation on the necessity of a REMS to mitigate the risks of embryo-fetal toxicity and hepatotoxicity, weighing such factors as the burden on stakeholders with the benefit-risk profile of sparsentan to determine the appropriate risk mitigation strategy. The review

team considered the estimated size of the at-risk population who would receive sparsentan, the seriousness of the disease, the expected benefit of treatment, the seriousness of the adverse events, the expected duration of treatment with sparsentan and that sparsentan is an NME. DRM and DCN also discussed whether labeling with a BW, and inclusions of the risks of hepatotoxicity and embryo-fetal toxicity in warnings and precautions would be sufficient to mitigate these risks. Given the at-risk population at time of diagnosis skews toward a younger age group, in the early 20's to 30's, the age range when pregnancies are likely to occur in patients who can get pregnant, the teratogenic effects seen in animal reproductive studies, and known embryo-fetal toxicity risk in the ERA-drug class, DRM and DCN determined a REMS would be necessary to mitigate the serious risk of embryo-fetal toxicity. Similarly, hepatotoxicity associated with sparsentan is a serious concern as imbalances in DILI signals with prolonged latency and positive rechallenges were observed in the clinical development program even with a small study population. Other considerations included potential drug-drug interactions due to sparsentan's CYP3A4 metabolism and inhibitor activities (i.e., due to increased accumulation of other drug metabolites or intra-hepatic sparsentan) that may contribute to liver injury, the limited size of the safety database making it difficult to evaluate the severity of hepatotoxicity, potential unfamiliarity of the prescriber population with monitoring for hepatotoxicity, and the known risk of hepatotoxicity with other drugs in the ERA drug-class. DRM and DCN agreed a REMS was necessary to ensure that the benefits outweigh the risks of hepatotoxicity associated with sparsentan.

DCN and DRM held multiple discussions on how to closely align the proposed Filspari REMS with the ERA REMS as both the ERA REMS and Filspari REMS have similar risks and utilize similar REMS elements to mitigate these risks. DRM and DCN recognized that the ERA and Filspari REMS impact different prescribers and patient populations. Overall, DRM and DCN agreed that the Filspari REMS should align with ERA REMS, when possible, to standardize REMS within similar drug-classes and similar risks.

Additionally, DRM proposed to incorporate gender neutral language in the Filspari REMS, as has been done with the isotretinoin REMS (iPLEDGE) and Qsymia REMS in order to ensure patient access regardless of gender identity. This aligns with CDER's current thinking of incorporating gender neutral language in newly established REMS for embryo-fetal toxicity to achieve health equality, eliminate disparities, and improve health in all groups as one of the health priorities in the Healthy People 2020 and 2030 initiatives. As a result of incorporating gender neutral language, all patients must be enrolled in the REMS to place them into two categories: patients who can get pregnant and patients who cannot get pregnant. To mitigate the risk of embryo-fetal toxicity, no other actions are necessary for patients who cannot get pregnant. The requirements that previously applied to females of reproductive potential would become requirements for patients who can get pregnant. The Ambrisentan and Macitentan REMS only enroll female patients, thus incorporating gender neutral language requiring enrollment of all patients imparts some additional burden that may be offset by reducing health disparities.

The review team also evaluated whether a registry in the REMS would be necessary to help characterize the severity of the liver injury associated with sparsentan versus having the Applicant conduct a study as a postmarketing requirement (PMR). It was concluded a PMR study would be necessary to detect and characterize DILI and liver-related adverse events with sparsentan as it will provide a more comprehensive method to gather the safety data than using a registry in the REMS. Further, the review

team will require an enhanced pharmacovigilance plan to detect hepatotoxicity signals in the postmarketing setting. As the severity of hepatotoxicity risk is not fully characterized, DCN will consider accruing clinical trial and postmarketing data that could lead to a re-evaluation of the need for a REMS with increasing certainty about the hepatic safety profile of sparsentan.

On August 1, 2022, a meeting of the REMS Oversight committee (ROC) was convened to discuss the need for a REMS for sparsentan to mitigate the risk of embryo-fetal toxicity and to obtain ROC's concurrence on the proposed REMS. The ROC concurred with the necessity of a REMS with ETASU and agreed with the changes proposed by the review team.[13 j] In addition, the ROC endorsed the use of gender-neutral language in the Filspari REMS. The Applicant agreed to incorporate gender-neutral language in the REMS and the proposed labeling in their response to the LCM meeting package.[22] The ROC was informed of the need to add the risk of hepatotoxicity to the Filspari REMS via a ROC email on September 27, 2022.[23] The ROC concurred with including the risk of hepatotoxicity in the Filspari REMS. The Applicant was informed in the LCM package of the Agency's determination that DILI is a potential serious risk, and a REMS would be necessary to ensure the benefits outweigh the risk of hepatotoxicity associated with sparsentan.[24]

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

As described above in section 7.1.1, the objectives align with public health prevention aims of primary prevention, prevent an event from occurring, and secondary prevention, emphasis on early event detection and focus on monitoring strategies to prevent worsening.

The Filspari REMS will consist of the following elements:

1. Prescriber certification (ETASU A) to ensure prescribers are educated about the risks, the need to enroll and counsel patients, and the need to monitor patients
2. Pharmacy certification (ETASU B) to ensure that prescribers are certified, patients are enrolled, and certain safe use requirements are met prior to dispensing
3. Safe Use Conditions (ETASU D) to ensure that Filspari is dispensed to patients who have been enrolled in the REMS, who have received counseling about the risks, reproductive status has not changed, and
4. Patient Monitoring (ETASU E) to ensure prescribers attest and document that they have completed monitoring of the patient's liver test and negative pregnancy status (for those who

[j] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

can become pregnant) as described in the Prescribing Information (i.e., pregnancy testing is to be performed in patients who can become pregnant prior to initiation, monthly during treatment, and one month after discontinuation of therapy; and liver testing is to be performed before initiation, monthly for the first 12 months, then every three months during treatment.)

The overall outcome measures to determine success of the REMS are the number of adverse events of hepatotoxicity and pregnancy events in patients on Filspari. However, given IgAN is a rare disease and affects a small population, it is not feasible to use these measures to accurately assess the success of the REMS program. The REMS is not designed or intended to collect test results. Instead, it provides a framework to support stakeholders in the safe use of the product. The REMS requires that prescribers assess liver and pregnancy testing results and that pharmacies verify that these tests were done with each dispense. We assume that if the tests were done that the prescribers will take appropriate action as described in the REMS training and labeling. Therefore, indirect measures such as compliance with verification that testing occurred may help assess the success of the goal in the Filspari REMS.

Key Performance Indicators

Key Performance Indicators (KPIs) are measures that are essential in determining that the REMS is functioning as designed, and whether the Filspari REMS is achieving its goal of mitigating the risks of hepatotoxicity and embryo-fetal toxicity. The KPIs have been established for each of the three objectives by developing a range of thresholds for specific assessment metrics that indicate if the REMS is functioning as designed or may help determine if modifications to the REMS are necessary.

The KPI thresholds for the Filspari REMS are based on our experience with the ERA REMS that meet similar performance thresholds. KPIs at or above the target threshold indicate the REMS is functioning as designed and is meeting the objective. KPIs above the minimum threshold but below the target threshold may alert that the REMS performance is not optimal and further investigation may be warranted to determine if other confounding factors are involved that impact compliance. The Applicant may need to conduct a root cause analysis (RCA) or deploy corrective and preventative actions (CAPAs). A KPI at or below the minimum threshold indicates that the REMS is not functioning as designed, is not meeting the objective, and may require a modification to meet the goal or other actions to improve compliance. DRM and DMAMES have taken into account the complexity of implementing a new REMS in determining the targeted thresholds. DRM and DMAMES acknowledge that the targeted thresholds based on experiences with other REMS with similar risks but for a different prescriber and patient populations, may not be truly representative of the IgAN patient population and further changes in the KPI thresholds may be warranted as we gain more experience with the Filspari REMS.

Table 1: Filspari REMS Key Performance Indicator Target Thresholds

REMS Objective	KPI	Thresholds
Monitor for elevations in liver enzymes in patients exposed to Filspari	% of all dispenses associated with confirmation from a certified pharmacy that liver	≥ 98% target threshold > 96% minimum threshold

	function testing was performed when required or the prescriber authorized the refill prior to each dispense	
Ensure that patients who can become pregnant are not pregnant before initiating Filsapri	% of all patients who can become pregnant have documentation of negative pregnancy test on the Patient Enrollment Form prior to treatment initiation	≥ 99% target threshold > 98% minimum threshold
Minimize exposure in patients who may become pregnant while taking Filsapri	% of all dispenses for patients who can become pregnant are associated with confirmation from a certified pharmacy that monthly pregnancy testing was performed, or prescriber authorized refill prior to each dispense	≥ 98% target threshold > 96% minimum threshold

DRM, DMAMES, DCN, and Office of Medication Error Prevention and Risk Management (OMEPRM) discussed and revised the KPIs to make them more specific and to reflect the REMS operations. Further, DRM and DMAMES considered how other REMS with similar risks, specifically, ERA REMS, assess their goals. DRM and DMAMES discussed the metrics needed for each of the objectives, where and how the data can be captured, and assumptions in determining the KPI measures and targeted thresholds.

Metrics in the KPIs are obtained from documentation in the ***Patient Enrollment Form*** and from required REMS verification data submitted to the REMS from certified pharmacies. The Filspari REMS is designed to have the pharmacist verify completion of liver and pregnancy testing with the patient or prescriber before each dispense, however it does not capture the test results. This REMS, as designed, assumes that if testing is verified to have been completed, the prescriber would have assessed the test results and adjusted the patient's treatment plan as necessary. The KPI is an indirect measure for the prescriber's adoption of the safe use behavior, monitoring for elevations in liver enzymes. DRM and DMAMES recognize the limitations on the robustness of the data based on having the patient confirm completion of required tests when asked by the certified pharmacy before each dispense versus having the actual test results submitted to the REMS or having the prescriber affirm assessment of monthly test results in the REMS. However, that level of data collection in the REMS was determined not to be necessary to mitigate the risks and may adversely impact the burden on the healthcare system and timeliness of patient access. We note that the REMS functioning as designed may not equate to actual testing being performed due to reliance on attestations and potential overrides. We will consider other potential sources of information such as hepatotoxicity or pregnancy reports from the PMR, FAERS, and

PADERs or claims database studies to further evaluate if testing is being performed appropriately per the Prescribing Information.

(b) (4)

The targeted threshold of 80% or greater for stakeholder knowledge is acceptable and consistent with other REMS with stakeholder knowledge assessments.

DRM concludes that based on the review of the proposed REMS received on February 13, 2023, the REMS will support actions that will mitigate the risks of hepatotoxicity and embryo-fetal toxicity. The REMS will ensure that all prescribers and pharmacists are trained on these risks and supports safe use of the product.

8.1. Key Risk Messages:

The following REMS materials will provide education and support the risk messages of the REMS:

- Prescriber Enrollment Form
- Patient Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Prescriber and Pharmacy Guide
- Patient Guide
- Change in Reproductive Potential Status Form
- REMS Website

Based on the objectives, key risk messages for **patients** include the following:

- There is a risk of embryo-fetal toxicity.
- Confirm that you are not pregnant by taking a pregnancy test before starting Filspari if you are a patient who can become pregnant.
- Use effective contraceptives and avoid pregnancy if you are a patient who can become pregnant. A pregnancy test is required before each refill.
- There is a risk of liver problems.
- Get liver tests monthly for one year and then every three months thereafter.

Based on the objectives, key risk messages for **prescribers** to know/understand are:

- Embryo-fetal toxicity can occur in patients taking Filspari. Confirm that patients who can become pregnant are not pregnant before initiating treatment.
- Counsel patient on the need for pregnancy testing monthly during treatment, and for one month after treatment. Instruct patients who can become pregnant to use effective contraceptives.

- Hepatotoxicity can occur in patients taking Filspari. Perform liver testing before initiating treatment and conduct monthly tests during treatment for 12 months, and then every three months during treatment with Filspari.
- Counsel the patient on the need for liver testing.

Based on the objectives, key risk messages for **pharmacies** to know/understand are:

- Confirm that the patient's reproductive status has not changed.
- Before each dispense, verify monthly pregnancy testing is complete and complete counseling on embryo-fetal toxicity for patients who can become pregnant.
- Before each dispense, verify that liver testing is complete, monthly during first year of treatment and every three months thereafter, and complete monthly counseling on hepatotoxicity during treatment.

9. Conclusion & Recommendations

The risks of hepatotoxicity and embryo-fetal toxicity associated with Filspari are serious and it is necessary for prescribers, pharmacists, and patients to understand these risks, and the importance of monitoring liver tests and pregnancy status before initiation and during treatment with Filspari. Based on the magnitude and severity of the risks, DRM and DCN agree that requiring a REMS consisting of prescriber certification, pharmacy certification, documentation of safe use conditions (patient enrollment, counseling) and monitoring patients for completion of liver and pregnancy testing (for patients who can become pregnant) is necessary to ensure that the benefits outweigh the risks. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's Proposed REMS received on February 13, 2023, to be acceptable and is appended to this review.

10. Appendices

10.1. Filspari REMS Assessment Plan

(b) (4)

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10.2. References

1. Travere Thereapeutics I. 2.7.3 Summary of Clinical Efficacy, dated March 20, 2022.
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21. Charuni S. OPDP Consult review for sparsentan NDA 216403, January 25, 2023.
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Division of Cardiology and Nephrology

NDA/BLA #s:	216403
PRODUCT:	Filspari (sparsentan) tablets
APPLICANT:	Travere Therapeutics
FROM:	Mary Ross Southworth, PharmD Deputy Director for Safety, Division of Cardiology and Nephrology
DATE:	February 16, 2023

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Filspari (sparsentan) to ensure that the benefits of the drug outweigh the risks of embryotoxicity and hepatoxicity. In reaching this determination, we considered the following:

A. Filspari (sparsentan) will be indicated for the treatment of immunoglobulin A nephropathy (IgAN). The estimated number of patients in the United States with IgAN is 169,000 (2:1 male-to-female predominance; occurs with the greatest frequency in East Asians and Caucasians and is relatively rare in individuals of African ancestry.)

B. IgAN is a rare and serious disease that is associated with high morbidity and mortality; peak incidence is in the second and third decades of life and approximately 40% of patients progress to end-stage kidney disease (ESKD) within 20 years of diagnosis. Symptoms include gross or microscopic hematuria, subnephrotic proteinuria, nephrotic syndrome, or an acute, rapidly progressive glomerulonephritis.

C. Filspari (sparsentan) has demonstrated an effect in reducing proteinuria in adults with IgAN who are at high risk of disease progression. The indication is being approved under accelerated approval and verification of an effect on kidney function decline will be required in the postmarketing setting.

D. Filspari (sparsentan) will be used chronically.

E. Filspari (sparsentan) may cause teratogenicity (based on animal studies) and hepatotoxicity (observed in clinical studies). It is contraindicated in pregnancy. The background incidence of adverse pregnancy outcomes in patients with IgAN is unknown; however, such patients are generally discouraged from becoming pregnant because of the significant risk of maternal and neonatal morbidity and mortality. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20%, respectively.

   Filspari (sparsentan) may cause hepatotoxicity. In clinical studies, Filspari caused elevation of liver aminotransferases, including cases with positive rechallenge. Other drugs in the endothelin receptor antagonist class have caused elevations of aminotransferases, hepatotoxicity, and liver failure. A precise incidence of severe hepatotoxicity in patients taking Filspari (sparsentan) is not known.

F. Filspari (sparsentan) is a new molecular entity.

The elements of the REMS will include elements to assure safe use, which include:

- Healthcare providers who prescribe the drug are specially certified.
- Pharmacies that dispense Filspari (sparsentan) are certified.
- Filspari (sparsentan) is dispensed only with documentation of safe use conditions, to include pregnancy and hepatic enzyme testing.
- Each patients using Filspari (sparsentan) is subject to certain monitoring.

The elements of the REMS will also include an implementation system and a timetable for submission of assessments of the REMS.

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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
PDUFA Goal Date	February 17, 2023
OSE RCM #	2022-567
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
	Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	February 10, 2023
Subject	Evaluation of Proposed REMS
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics
Therapeutic Class	Endothelin and angiotensin receptor antagonist
Formulation(s)	200 mg and 400 mg oral film-coat tablet
Dosing Regimen	200 mg once daily for 14 days then increase to 400 mg once daily, as tolerated

Table of Contents

1. Introduction

This review evaluates the amendment to the proposed risk evaluation and mitigation strategy (REMS) submitted on February 9, 2023, for the new molecular entity (NME) Filspari (sparsentan). Travere submitted a New Drug Application (NDA) 216403 for Filspari (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older.

The Applicant's REMS proposal is not acceptable as further edits are needed to align the REMS materials with the REMS Document and accompanying attestations cleared by the Office of Chief Counsel.

DRM and DMAMES met on February 8, 2023 to discuss the Assessment Plan. There are no substantive changes to the assessment plan submitted by the Applicant on February 3, 2023. The final Assessment Plan is appended to the review and will be communicated to the Applicant.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for sparsentan (NDA 216403) relevant to this review:

- 1/27/2023: Travere submitted an REMS amendment in response to the Agency's IC3 and IR from January 18 and 19, 2023 (eCTD seq. no. 48).

- 2/3/2023: The Agency provide interim comments (IC4) to the Applicant in response to their REMS amendment, dated January 19, 2023.

- 2/8/2023: Travere submitted a courtesy copy of the REMS amendment via email.

- 2/9/2023: The Agency held a teleconference with the Applicant to discuss the status of the REMS review and to answer questions they may have in order to gain alignment on an approvable REMS.

- 2/10/2023: Travere submitted a formal REMS amendment in response to the Agency's IC4 from February 3, 2023 (eCTD seq. no. 53).

3. Comments for the Applicant

Further changes to the REMS are required to be acceptable

The following comments and attached redlined Filspari REMS materials are based on our review of the proposed REMS submitted by Travere on March 20 and amended June 9, October 13, December 12, December 19, 2022, and January 27, 2023, February 3, 2023, and February 9, 2023. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment by **COB Tuesday February 14, 2023**. These comments should not be considered as the final edits to the REMS. The REMS Document and all REMS materials must align with the final approved labeling.

General comments:

We find your clarifications on the pharmacy REMS verification process, addition of reminders in the REMS materials and REMS portal to ensure compliance with safe use conditions, and the added information to the REMS website/post login screens to be acceptable.

However, further edits in the selected REMS materials are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions (PDF and Word versions) of the REMS materials should align.

As labeling negotiations are ongoing, language in the REMS may be subject to further changes to align with labeling.

REMS Document

- We are providing a clean MS Word version for you to incorporate into your next REMS amendment submission. We ask that you do not change or include further additions, if possible.
- We are also providing a separate document with the stakeholder attestation statements. Align the attestation statements throughout all impacted REMS materials.

REMS Supporting Document (RSD)

The clarifications and changes in the RSD are acceptable. The additional screenshots of the post login screens are acceptable.

Align the RSD to the final REMS Document and attestations.

REMS Assessment Plan

Overall, the Assessment plan metrics are acceptable. However, some editorial changes made, including re-ordering the assessment metrics were not necessary and were not accepted. The final version is attached.

REMS materials

See attached redlined documents. Redlined changes have been made to align the materials with the final REMS Document and attestations. Review the changes and ensure they align with the changes in the REMS Document and the attestation statements. Any further changes outside of our comments or additions to the materials could impact approvability of the REMS.

Submit your REMS amendment that includes revised REMS materials **by COB Tuesday February 14, 2023**. Accept the track changes in the MS Word newly redlined documents in your next submission. Also include a compiled PDF version of the REMS with all the REMS materials attached in the order they are listed in the REMS 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	Tracked MS Word Clean MS Word, PDF version
6	Inpatient Pharmacy Enrollment Form	Tracked MS Word, 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
9	Change in Reproductive Potential Status Form	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

4. Appendix

REMS Document

Enrollment Forms

1. Prescriber Enrollment Form
2. Patient Enrollment Form
3. Outpatient Pharmacy Enrollment Form
4. Inpatient Pharmacy Enrollment Form

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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
PDUFA Goal Date	February 17, 2023
OSE RCM #	2022-567
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
	Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	February 3, 2023
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1. Introduction

This review evaluates the amendment to the proposed risk evaluation and mitigation strategy (REMS) submitted on January 27, 2023, for the new molecular entity (NME) Filspari (sparsentan).[1] Travere Therapeutics (Travere) submitted a New Drug Application (NDA) 216403 for Filspari (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This application is under an accelerated approval review in the Division of Cardiology and Nephrology (DCN). The Applicant proposed a REMS to mitigate the risk of embryofetal toxicity and hepatotoxicity. The Applicant's proposed REMS is similar to other ERA REMS for pulmonary arterial hypertension (PAH) and consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of sparsentan outweigh the risk of embryo-fetal toxicity and hepatotoxicity.

In this amendment, the Applicant provided further clarifications to the Agency's January 18 and 19, 2023, information requests (IRs)[a] and consisted of:

1. Added requirement that an inpatient pharmacy must obtain authorization from the REMS before dispensing Filspari and clarified that all certified pharmacies will need to confirm completion of pregnancy and liver tests with the initial dispense.
2. Added descriptions of an Office Contacts Management's role and responsibilities, how safe use requirements are captured and documented in the daily dispensing file, how patients/legal guardians can complete the enrollment process outside of the prescriber's office, what happens if the prescriber tries to submit an incomplete ***Patient Enrollment Form***, and responsibilities of the REMS Coordinating Center related to shipment delays.
3. Clarified possible actions taken by the REMS if the prescriber does not confirm a negative pregnancy test and/or did not confirm reviewing the patient's current liver testing in the ***Patient Enrollment Form*** submitted to the REMS.
4. Updated post-login screenshots for consistency and to align with updates to individual REMS forms
5. Removed (b) (4) from the attestations in the ***Inpatient Pharmacy Enrollment Form***.

The Applicant made global changes to the REMS to align with the proposed labeling for consistency across REMS tools. These changes include:

- Updated the presentation of risks throughout the REMS to align with current labeling.
    - Re-ordered listing of risks of hepatotoxicity ahead of embryo-fetal toxicity when listed together and updates to the REMS goal statement and the presentation order of the REMS objectives to reflect this change.
    - Revised all references related to frequency of liver testing from "(b) (4) " to "monthly for the first 12 months, then every 3 months during treatment".

[a] IRs emails to Travere, dated January 18 and 19, 2023.

- Updated "[redacted]" to "Patient Enrollment Form" and "[redacted]" to "Prescriber Enrollment Form" to align with the nomenclature of materials across REMS.
- Editorial changes and formatting updates based on the REMS Document Technical Conformance Guide (e.g., added Section VI. Statutory Elements that listed the elements of the REMS.

In addition, Travere agreed to submit certifications of translations for the Patient Enrollment Form and the Patient Guide, as they will be available in different languages (English, Spanish, and Chinese) as a REMS correspondence no later than 30 days after REMS approval.

Further clarifications are needed on the requirement for the pharmacy to obtain an authorization code to dispense, impact of the requirement for inpatient pharmacy to obtain authorization to dispense on patient access, and the differences in "[redacted]" and "[redacted]" used throughout the REMS, as the information presented in the REMS Document, REMS supporting Document, and REMS Website appears to be inconsistent. Travere did not update the ***Patient Enrollment Form*** to include pregnancy and liver testing dates, as requested in the Agency's IR, however, in lieu of collecting the date of required testing, further language in REMS materials is needed to educate pharmacists to confirm completion of required testing since the last refill. Travere will need to further clarify the option for prescribers and pharmacies to allow for an one-time override authorization to dispense. Additionally, the REMS Document requires further revisions to align with current thinking on the presentation and flow of information. The Applicant will need to align the changes in the REMS Document throughout the REMS (REMS Supporting Document, REMS materials and REMS website). The Key Performance Indicators (KPIs) and targeted thresholds are revised to make them more specific and better reflect the REMS operations. Lastly, further updates and edits are needed throughout the REMS to align with draft labeling and the Medication Guide.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for sparsentan (NDA 216403) relevant to this review:

- 1/18, 2023: The Agency sent interim comments (IC3) to the Applicant in response to their REMS amendment, dated December 19, 2022.
- 1/19, 2023: The Agency sent via email further information requests to the Applicant.
- 1/27/2023: Travere submitted an REMS amendment in response to the Agency's IC3 and IR from January 18 and 19, 2023 (eCTD seq. no. 48).

3. Discussion

The Applicant submitted a REMS amendment on January 27, 2023 that added a requirement for inpatient pharmacies to obtain authorization prior to dispense, clarified processes such as how a certified pharmacy obtains a 'REMS verification code' and how the REMS captures daily dispense data, provided further information on the patient enrollment processes (including scenarios of submission of incomplete patient enrollment forms), detailed responsibilities of the REMS Coordinating Center, and expanded on the role of the office contact management.

Travere added a requirement for inpatient pharmacies to obtain authorization before dispensing to allow the pharmacy to document that REMS requirements were met (i.e., that the patient is enrolled or will be enrolled prior to discharge and under the supervision and care of certified prescriber, that the liver testing is complete, counseling on hepatotoxicity is complete, and patient's reproductive status has not changed). Travere also indicated that pharmacies are unable to obtain authorization to dispense without confirming liver testing and pregnancy testing is complete (at initiation and monthly). Travere reiterated certified pharmacies agree to the comply with REMS requirements at the time of certification and to establishing processes and procedures to ensure safe use requirements are met prior to dispense. As a verification code for dispensing cannot be provided without verification of testing completion, Travere indicated that reminder messages to ensure safe use conditions have not been incorporated into the REMS Verification Portal, as confirmation of completion of safe use requirements (or confirmation of an override of these requirements) is included in the daily dispending file sent electronically to the REMS. The REMS monitors data received from the pharmacies to ensure REMS requirements have been met. The REMS Coordinating Center (RCC) is responsible for conducting a root cause analysis upon identification of a shipment delay due to reporting a missed pregnancy test and/or liver testing.

Travere provided descriptions of scenarios involving incomplete patient enrollment submissions and situations when the patient enrollment form submitted by the prescriber indicates "No" on confirmation of negative pregnancy test or "No" on having confirmed assessment of liver test results prior to initiation of treatment with Filspari. Prescribers will not be able to submit the ***Patient Enrollment Form*** online if there are any missing required fields. If the prescriber submits an incomplete ***Patient Enrollment Form*** via fax to the RCC, the RCC will contact the prescriber to obtain missing required data***.*** If the prescriber marks "No" to confirming a negative pregnancy test and or "No" to assessing liver test results in the ***Patient Enrollment Form***, the online REMS application includes logic to not allow enrollment to be completed without this confirmation. If the RCC receives a ***Patient Enrollment Form*** via fax and the prescriber answered "No" to confirming a negative pregnancy test, or "No" to confirming assessment of liver test results, the RCC will inform the prescriber that the patient is unable to be enrolled without that confirmation. A revised ***Patient Enrollment Form*** indicating that a negative pregnancy test and or assessment of liver test results have been confirmed would be required to enroll the patient in the REMS. In both modalities for patient enrollment, the patient will not be enrolled until all required fields are entered.

Travere clarified that the role of the "Office Contact Management" personnel only serves to facilitate communication between the REMS Program and they do not have the ability to complete ***Patient Enrollment Forms*** or submit ***Change in Reproductive Potential Status Forms*** on behalf of the prescriber,

assess required laboratory results or provide an override to authorize dispensing of Filspari when required liver monitoring is not confirmed.

The Applicant made global changes to the REMS to align the proposed labeling and to align the name of selected REMS materials (i.e., ***Patient Enrollment Form*** and ***Prescriber Enrollment Form***) with other nomenclature of materials across REMS. One of the global changes involved reordering the presentation of the two REMS risks to align with the order they appear in labeling; Travere updated the REMS goals placing the risk of hepatotoxicity before embryo-fetal toxicity risk and in turn, the REMS objectives were re-aligned to reflect the order of the risks.

Upon review of the proposed changes to the REMS, further clarifications are needed for the REMS to be acceptable, specifically, on the requirement and process for an inpatient pharmacy to obtain a REMS verification code to dispense as it may impact timely patient access. Travere will need to clearly describe differences in processes for obtaining the authorization code in the inpatient setting versus outpatient pharmacy setting, if any. Outpatient pharmacies include documentation of safe use requirements in their daily dispensing file that is sent to the REMS, but it is not clear how an inpatient pharmacy communicates to the REMS that the safe use requirements to ensure safe use are met. In addition, how the daily dispensing files are transmitted to the REMS would need to be defined. Though a one-time override for prescribers to authorize dispensing when completion of required testing is not confirmed and for certified pharmacies to dispense for supply greater than 30-days is allowed, further clarification is needed on whether this is a one-time override through the lifetime of the patient in the REMS or whether there are other criteria and timeframes when an override is allowed. Differences in terminologies used throughout the REMS such as "(b) (4)" and "(b) (4)" will need to be clearly defined as they may be interpreted differently. Consistency in usage of these terms should be applied throughout the REMS to reduce confusion.

The Applicant will need to clarify inconsistencies in the processes described with regards to when a pharmacy obtains an authorization to dispense upon fulfillment of the REMS requirements. The information presented in the REMS Document, REMS Supporting Document, and REMS Website indicated that the 'REMS authorization code' generated via the REMS portal by the inpatient and outpatient pharmacy only serves to verify prescriber certification and patient enrollment. The pharmacist must also confirm the other safe use requirements (i.e., completion of required pregnancy/ liver tests, complete counseling on risks, and confirm patient's reproductive status has not changed) via the processes and procedures developed and implemented by the individual pharmacy. The Applicant, however, provided in their responses to 1/18/2023 and 1/19/2023 IRs that the pharmacy will not be able to obtain authorization to dispense from the REMS if all requirements are not met (verification of patient enrollment, prescriber certification, completion of counseling, confirmation of pregnancy/ liver testing, and confirmation of reproductive status has not changed). This description aligns with a common concept in other REMS programs of a 'REMS dispense authorization', or RDA, where the process of obtaining an RDA from the REMS portal incorporates verification of all safe use conditions as previously entered into the REMS program. Because the Filspari REMS is not designed to capture all safe use conditions in the REMS portal, language around this concept should be harmonized throughout the REMS to reflect what the 'REMS verification code' includes and to define the other safe use

conditions that should be met. Additionally, the REMS portal as designed does not provide a prompt or indication to the dispensing pharmacy that they should also be verifying other safe use conditions with every dispense, in addition to generating the 'REMS verification code'. Additional language around this should be added to the REMS portal screenshots for the pharmacy workflow, and in the ***Prescriber and Pharmacy Guide*** to educate the pharmacy.

Travere did not include pregnancy and liver test dates in the ***Patient Enrollment Form*** as requested in by the Agency, citing a lack of a specific timing requirement for required testing in the products label or REMS Document. However, incidences may arise where the patient may be enrolled but experiences a delay in starting Filspari. The patient may be at risk when required pregnancy and/or liver testing is not recent. We agree with the pharmacy confirming testing prior to first dispense to ensure that there is a current test result, however, in lieu of documenting the dates for required testing, the Applicant should add language in the ***Prescriber and Pharmacy Guide*** to educate the pharmacy that with every dispense of Filspari, they should confirm required testing has been done since their last dispense. A similar reminder should also be incorporated in the pharmacy website screenshots. Additionally, the Applicant should describe in the REMS Supporting Document how much time may lapse before a patient enrollment form is no longer valid if a patient does not receive their first dispense of Filspari.

Further revisions are required in the REMS. KPIs and their targeted threshold were revised to make them more specific to the REMS and to better reflect the REMS operations as designed. The KPIs metrics are used to assess the success of the REMS in mitigating the risks of hepatotoxicity and embryo-fetal toxicity. The changes in the targeted threshold provided flexibility in achieving the targeted goals to account for complexity with initiating a new REMS. The Applicant will need to incorporate the revised KPIs and targeted thresholds into the REMS Supporting Document. The final review will include further details. The REMS Document requires further revisions to improve the presentation and flow of information. The Applicant will need to align the changes in the REMS document throughout the REMS (REMS Supporting Document, REMS materials and REMS website).

Lastly, further updates and edits are needed throughout the REMS to align with labeling and Medication Guide.

4. Conclusions and Recommendation

DRM does not find the Filspari REMS as submitted on March 20, 2022, and amended on June 9, October 13, December 19, 2022, and January 27, 2023 to be acceptable. DRM recommends the comments in Section 5 be sent to the Applicant.

5. Comments for the Applicant

The following comments and attached redlined Filspari REMS materials are based on our review of the proposed REMS submitted by Travere on March 20 and amended June 9, October 13, December 12, December 19, 2022, and January 27, 2023. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment within **3 business** days of receipt, by **12**

Noon, February 7, 2023. These comments should not be considered as the final edits to the REMS. The REMS Document and all REMS materials must align with the final approved labeling.

With the goal date approaching, the Agency is open to scheduling an ad hoc teleconference next week to discuss further amendments to the REMS so that we may come to alignment and finalize review of your proposed REMS. Please let Anna Park, Senior Regulatory Project Manager, know if you would like to schedule a teleconference by **COB Thursday February 6, 2023**.

General comments:

We agree with global changes in the REMS to reorder presentation of the risk information to align with labeling and acknowledge the information provided on the responsibilities, descriptions of actions taken by the REMS for incomplete, missing required data or lack of confirmation of required testing in the ***Patient Enrollment Form***, and find the details provided to be acceptable.

However, further clarifications and edits in the selected REMS materials are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions (PDF and Word versions) of the REMS materials should align.

As labeling negotiations are ongoing, language in the REMS may be subject to further changes to align with labeling.

REMS Document

Reorder the presentation of the REMS requirements to align with the order of risks presented in the REMS goals and labeling, i.e., hepatotoxicity requirements followed by embryofetal toxicity requirements. This should also be applied throughout the REMS wherever the REMS requirements are presented.

We require further information on the requirement of the inpatient pharmacy to obtain an authorization to dispense and its impact on patient access. Please see REMS Supporting Document section for more details.

We agree with the addition of Section VI. Statutory Elements to the REMS Document as this aligns with the 2023 REMS Document Technical Conformance Guide. However, based on internal review, we have further edits to the REMS Document to streamline, and improve consistency and flow of information. See attached redlined document.

REMS Supporting Document (RSD)

Provide details on the following in the RSD and in Appendix 3: Post Login Screens (PDF version):

1. Clarify how requiring an inpatient pharmacy to obtain an a 'REMS verification code' to dispense impacts patient access, as patients may not yet be enrolled in the REMS at the time of dispensing, or the prescribing physician in the facility may not be certified at the time of prescription, e.g., a resident continuing a patient's home medications. It is unclear how a 'REMS

verification code' is generated if the prescriber is not certified in the REMS – does the scenario provided allow for a patient who is enrolled by a certified prescriber but the 'non-certified prescriber' in your screenshot is the inpatient facility prescriber?

2. Describe any differences in the obtaining of authorization to dispense for inpatient versus outpatient pharmacies. Outpatient pharmacies are required to document and submit safe use requirements, and it appears they do this in their daily dispensing file that is sent to the REMS. Clarify how the inpatient pharmacy will report verification of these safe use requirements to the REMS. If the process is the same, then the language in the REMS Document and REMS Supporting Document for obtaining authorization by the outpatient and inpatient pharmacies should be consistent.

3. Define the difference between "(b) (4)" and "(b) (4)." These terms are used in the REMS Document, REMS Supporting Document/REMS post login screens and may be interpreted differently and cause confusion. Because the REMS verification code does not provide a verification of all safe use conditions, it should not be referred to as an authorization to dispense. Consistency in usage of these terms should be applied throughout the REMS to reduce confusion.

4. Clarify inconsistencies in the fulfillment of the safe use requirements when the pharmacy obtains an authorization to dispense. The information presented in the REMS Document, REMS supporting Document, and REMS Website indicated that the authorization code/ verification code serves to confirm that the prescriber is certified, and the patient is enrolled in the REMS, and once these are confirmed, the REMS generates the authorization code for the pharmacist to dispense. The pharmacist must confirm the other the safe use requirements (completion of required pregnancy/ liver tests, complete counseling on risks, and confirm patient's status has not changed). However, you stated in your responses to the 1/18/23 and 1/19/23 IRs that an authorization code for dispensing cannot be provided without verification of testing completion. The REMS verification portal for the pharmacy does not show there is verification of testing completion. Add detail to the Prescriber and Pharmacy Guide for the dispensing pharmacy on what steps must be taken to verify the safe use conditions are met with every dispense, indicate that the pharmacist should ensure required testing has been completed since the last dispense of Filspari, and add language to the pharmacy post login screens to prompt the pharmacy to ensure all safe use conditions have been met, in addition to obtaining the REMS verification code.

5. Clarify post login screens (90 and 93) depicted in the REMS Supporting Document, Appendix 3. These screens show the inpatient pharmacy successfully obtaining the REMS verification code, for 1) when the patient is not enrolled and prescriber is certified, and 2) for when the patient is enrolled, and prescriber is not certified. We agree that the inpatient pharmacy should be able to obtain a verification code for these scenarios, however, this appears counter to the definitions of verification/authorization code that verifies patient enrollment and prescriber certification before an authorization code can be generated. The REMS does allow patients in the inpatient

setting to be enrolled or to receive drug so long as they will be enrolled prior to discharge. If only certified prescribers can enroll a patient, clarify who is listed as the prescriber (not certified) in the screen (page 93) and whether it reflects entry of information for a prescriber in the hospital setting who may not be certified or if it is linked to a different prescriber.

6. Clarify how the Daily Dispensing File will be transmitted electronically (via fax, REMS link, email, or other methods) to the REMS (i.e., what format and data fields are included).

7. The limitation for the "Office Contact Management" is incomplete. The "Office Contact Management" personnel should not be able to provide an override to authorize dispensing when required pregnancy test in addition to liver test are not confirmed.

8. We understand that prescribers may provide a one-time override authorization to dispense Filspari if testing has not been completed, and for certified pharmacies to dispense greater than a 30-days' supply with a documentation of reason. Clarify if the onetime override (unconfirmed testing and supply greater than 30-days') occurs over the lifetime of the patient in the REMS or are there other timeframes and criteria for an override.

9. Provide detail on how much time may lapse between enrollment of a patient and the first dispense of Filspari before a patient is not considered 'enrolled' and qualified to receive drug per the 'REMS verification code' process.

10. Key Performance Indicators (KPIs) are measures which are essential in determining the success of the Filspari REMS, ensures that the REMS is functioning as designed, and support the determination of whether the Filspari REMS is achieving its goal of mitigating the risks of hepatotoxicity and embryo-fetal toxicity. Upon further review, we revised the KPIs and their targeted thresholds to make them more specific and to reflect the REMS operations. Given this is a new REMS, we have provided ranges for interpreting the KPI's in measuring the overall performance of the REMS. Further changes to targeted thresholds may be considered after we gain more experience with the Filspari REMS. Include the KPIs and targeted thresholds from the attached document in a new section, titled "Key Performance Indicators" before Section 4 (REMS Assessment Plan) in the REMS Supporting Document.

Assessment Plan

- Comments were provided in a separate communication.

Patient Enrollment Form

- We acknowledge your rationale for not including a test date for the pregnancy and liver results in the ***Patient Enrollment Form***. We understand that the proposed REMS Document, labeling, and other similar REMS do not require collection of test dates in the enrollment form. However, we have concerns that incidents may arise where the patient may be enrolled but delays initiating Filspari treatment. The patient may be at risk without checking for more current testing. The Agency believes documentation of the test dates would enable assessment of

whether the REMS program is operating as intended to mitigate the risks by ensuring that the test results are current - it is not necessary to describe the need for a test date in the REMS Document or labeling as this is a process requirement. At this time, we accept the Form without the dates of testing, but in lieu of collecting the date of required testing, incorporate language in the Prescriber and Pharmacy Guide and in the post login screens for the pharmacy that educate the dispensing pharmacy that verification of test results takes place prior to the first dispense and since the last dispense have been completed (i.e. monthly, or within the last 3 months when a patient is more than 12 months out from initiating Filspari).

- We revised the statement (b) (4) to be contacted by the REMS if pregnancy occurs to a statement of understanding (b) (4) . Align other relevant REMS materials with this change (Prescriber and Pharmacy Guide and Patient Guide). See attached redlined document.

Inpatient Pharmacy Enrollment Form

- We acknowledge your acceptance of the edits to the form.

Prescriber and Pharmacy Guide

- Add detail to the Pharmacy section to emphasize the pharmacy should verify required testing has been done prior to first dispense and since the last dispense of Filspari (and within the last three months for liver testing after the first 12 months of therapy).
- Incorporate edits to align with labeling. See attached redlined document.

Patient Guide

- Incorporate edits to align with the Medication Guide. See attached redlined document.

REMS Website

- We acknowledge that you will be providing certifications of translation for the ***Patient Enrollment*** (b) (4) ***Form*** and the ***Patient Guide*** for the different languages (English, Spanish, and Chinese) no later than 30 days after the REMS approval which will be submitted as a REMS correspondence.
- Align the REMS website with changes to the REMS.

Submit a REMS amendment that includes revised REMS materials **within 3 business days by February 6, 2023**. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). 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 (b) (4) 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	Tracked MS Word Clean MS Word, PDF version

6	Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber and Pharmacy Guide	Tracked MS Word Clean MS Word, PDF version
8	(b) (4) Patient Guide	Tracked MS Word Clean MS Word, PDF version
9	Change in Reproductive Potential Status Form	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

6. Appendix

REMS Document

Enrollment Forms

1. Patient Enrollment Form

Training:

2. Prescriber and Pharmacy Guide
3. Patient Guide

7. References

1. Travere. Response to IRs 32 and 33, January 27, 2023 (eCTD sequence number 48).

37 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

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02/03/2023 01:33:28 PM

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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
Submission Type/Number:	Original-1/42
OSE TTT#	2022-2222
Reviewer:	Joseph Paradis, PharmD (DMAMES)
Team Leader:	Shelly Harris, ScD, MPH (DMAMES)
Associate Director:	Jo Wyeth, PharmD (OMEPRM)
Review Completion Date:	January 30, 2023
Subject:	Interim Comments for the Filspari (sparsentan) Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan for the Proposed New REMS
Trade Name:	Filspari
Established Name:	Sparsentan
Name of Applicant:	Travere Therapeutics
Appendix 1.	
Therapeutic Class:	Endothelin Receptor Antagonist (ERA)
Formulation(s):	200 mg and 400 mg oral film-coat tablet
Submission Date:	October 13, 2022, December 19, 2022

1. Introduction

This review is in reference to the proposed risk evaluation and mitigation strategy (REMS) Assessment Plan for the proposed REMS for Filspari (sparsentan).

The Applicant submitted a New Drug Application (NDA 216403) for Filspari (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This application is under an accelerated approval review in the Division of Cardiology and Nephrology (DCN). The Agency determined a REMS was necessary to mitigate the risks of embryo-fetal toxicity and hepatotoxicity.

2. Background

This section provides relevant regulatory history and the Filspari REMS proposed goal, elements, and timetable for submission of assessments.

2.1. Regulatory History

- March 20, 2022: NDA 216403 submitted for the treatment of IgAN in adults aged 18 years and older.
- June 28, 2022: The Agency held a Mid-Cycle meeting (MCM) with the Applicant via teleconference. The Agency informed the Applicant that we agreed with the necessity for a REMS to mitigate the risk of embryo-fetal toxicity. The Applicant was also informed that an imbalance in hepatotoxicity events is under review.
- September 1, 2022: Late Cycle meeting background package sent to the Applicant informing them of the Agency's determination that drug induced liver injury (DILI) is a potential risk for sparsentan. The Applicant was informed of the need to describe this risk in labeling and submit an amendment to the proposed REMS to include a goal, elements to assure safe use (e.g., monthly liver testing), and an implementation system to mitigate the risk of hepatotoxicity. The Applicant was also informed that labeling would need to align with the gender-neutral language in the REMS.
- September 12, 2022: The Agency held a Late Cycle teleconference with the Applicant. The Agency reaffirmed the necessity of a REMS to mitigate the risk of hepatotoxicity. The Applicant is to submit an amendment to the proposed REMS.
- October 13, 2022: The Applicant submitted a proposed REMS which included revisions to materials to incorporate the risk of hepatoxicity, including a REMS Supporting Document that contained the assessment plan.
- November 14, 2022: The Agency sent an Information Request to require liver function test monitoring on a monthly basis to mitigate the risk of hepatotoxicity.
- November 29, 2022: The Applicant responded to the Agency's November 14, 2022 Information Request proposing monthly liver function test monitoring for the first year, then quarterly thereafter.
- December 7, 2022: The Agency agreed to the November 29, 2022, proposed schedule of liver function test monitoring monthly for the first year, and then quarterly.
- December 19, 2022: The Applicant responded to the December 13, 2022 Information Request, and agreed with the revised goal, objectives, and (b) (4), and submitted a revised assessment plan.

2.2. REMS Goal, Elements, and Timetable for Submission of Assessments

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

- Objective 1: Monitor for elevations in liver enzymes in a patients exposed to Filspari
- Objective 2: Ensure that patients who can (b) (4) pregnant are not pregnant before initiating Filspari
- Objective 3: Minimize exposure in patients who may become pregnant while taking Filspari

The REMS elements include:

- Elements to Assure Safe Use
  - (b) (4)
- Implementation System[a]
  - Establish and maintain a REMS Website (www.FilspariREMS.com) that will include the capability to complete prescriber and inpatient pharmacy certification online, the capability to enroll and manage patients online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Website. The REMS Website must not link back to the promotional product website(s).
  - Make the REMS Website fully operational and all REMS materials available through website and REMS Coordinating Center at the time Filspari first becomes commercially available.
  - Establish and maintain a REMS Coordinating Center for REMS participants.
  - Establish and maintain a validated, secure database of all REMS participants who are enrolled and certified in the REMS.
  - Verify the name and contact information of the pharmacy's Authorized Representative every two years. If different than the current Authorized Representative on file, the pharmacy is required to recertify with a new Authorized Representative.
  - Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Filspari distribution and dispensing; certification

[a] See the Supporting Document for additional information on the Implementation System (available at: \\CDSESUB1\EVSPROD\nda216403\0044\m1\us\rems-supporting-doc-v3-20221217-redline.docx.

of prescribers, pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.

- Establish a plan for addressing noncompliance with REMS requirements.
- Monitor prescribers, pharmacies, and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
- Audit all certified outpatient pharmacies and wholesaler-distributors within 180 days after they become certified to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.
- Audit annually: 1) all certified outpatient pharmacies, 2) a representative sample of inpatient pharmacies that have ordered Filspari in the past year, 3) all wholesaler-distributors, and 4) the REMS Coordinating Center to ensure that all the REMS processes and procedures are in place, functioning, and support the REMS requirements.
- Take reasonable steps to improve implementation of and compliance with the requirements in the REMS based on monitoring and evaluation of the REMS.

The timetable for submission of assessments of the REMS is annually from the date of approval.

3. REMS Assessment Plan

We reviewed the proposed Filspari REMS Assessment Plan submitted on October 13, 2022.[b] The proposed REMS assessment plan includes metrics under the following categories: Program Implementation and Operations, Compliance, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes, and Knowledge. The metrics included in the proposed assessment plan were developed by the Applicant based on metrics from assessment plans for other REMS that mitigate similar risks (embryo-fetal toxicity, and hepatotoxicity), have similar REMS requirements, and elements to assure safe use. The proposed metrics are necessary to evaluate if the REMS is operating as intended and meeting its goal of mitigating the risk of embryo-fetal toxicity and hepatotoxicity by meeting its stated objectives.

(b) (4)

The proposed REMS assessment plan submitted by the Applicant on October 13, 2022 included proposed (b) (4)

On December 13, 2022, the Division of Risk Management (DRM) sent an Information Request with several comments regarding the Key PREMS materials, and the REMS goal, objectives and (b) (4). The

[b] The proposed REMS assessment plan was included in the Supporting Document submitted on October 13, 2022 (available at: \\CDSESUB1\EVSPROD\nda216403\0042\m1\us\rems-supporting-doc-draft-v2-20221012-redline.docx.

Applicant responded on December 19, 2022 and accepted the revised goal, objectives and proposed (b) (4) and submitted a revised assessment plan. (b) (4)

(b) (4)

Upon further discussion between DMAMES and DRM, we decided that the (b) (4) will not be included in the assessment plan. (b) (4)

Reviewer Comments:

Overall, the Agency agrees with the metrics incorporated into the assessment plan by the Applicant and has the following specific recommendations for revisions:

- *Certification and Enrollment Statistics are to be revised to reflect prescribers and pharmacies that are newly certified, total certified, and total certified that are active (prescribing or dispensing Filspari).*

- *Gender neutral language has been incorporated in all metrics by the Applicant that refer to "(b) (4)," and "(b) (4)" and have been revised to "patients who can become pregnant," and patients who cannot become pregnant."*

- *Program Implementation and Operations, Safe Use Behaviors, and Health Outcomes and/or Surrogates of Health Outcomes metrics are to be reported for the two previous, current, and cumulative reporting periods.*

- *For Program Implementation and Operations metrics, specific Program Implementation metrics for the first assessment are required to be added to report the Filspari REMS Program Launch Date, date when Filspari REMS Program materials became available, date stakeholders could enroll, and date when the Filspari REMS Program Website went live.*

- *For Infrastructure and Performance metrics related to the REMS Coordinating Center, in order to align with other new or revised REMS, the Agency is adding a metric to document any burden reported to the REMS.*

- *Age ranges for utilization metrics are being modified to align with other REMS that are designed to mitigate similar risks.*

- *Metrics to collect additional information on compliance including one time authorization, system interruptions, and any barriers or delays in dispensing have been added.*

- *Metrics to report* (b) (4) *are not necessary to be included in the assessment plan. Based on discussions with the review team, the Applicant will report* (b) (4) *using other required processes (e.g., postmarket study or commitment, enhanced pharmacovigilance). The Applicant will be instructed to remove them at this time.*

- *Revisions have been made to Knowledge metrics to clarify healthcare prescriber, pharmacist, and patient knowledge expectations, removal of* (b) (4)

4. Conclusions and Recommendations

The December 19, 2022 proposed Filspari REMS modification included a revised REMS assessment plan. We have additional comments on the proposed revisions.

5. Comments For The Applicant

We have the following comments on your proposed REMS Assessment Plan submitted on December 19, 2022. Review of the REMS proposal is ongoing; these comments should not be considered final.

Submit a REMS amendment within three business days that addresses these comments. Include in your response an updated REMS Supporting Document containing your revised REMS Assessment Plan; include a Word tracked changes version, a Word clean version, and a PDF version.

1. Program Implementation and Operations, Safe Use Behaviors, and Health Outcomes and/or Surrogates of Health Outcomes metrics are to be reported for the two previous, current and cumulative reporting periods, where applicable, unless otherwise noted.
2. For Program Implementation and Operations metrics, specific Program Implementation metrics for the first assessment are required to be added to report the Filspari REMS launch date, date when Filspari REMS materials became available, the date stakeholders could enroll, and date when the Filspari REMS Website went live.
3. A metric was added to the Program Implementation and Operations section to 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, health care availability, or other issues.
4. Age ranges for utilization metrics are being modified to align with other REMS that are designed to mitigate similar risks.
5. (b) (4) have been removed from the assessment plan and replaced with metrics to measure compliance with REMS requirements for pregnancy and liver function testing. (b) (4)

(b) (4)

6. Metrics to collect additional information on compliance, one time authorizations, system interruptions, and any barriers or delays in dispensing have been added.
7. Metrics to report (b) (4) have been removed from the assessment plan.
8. Revisions are recommended for Knowledge metrics to clarify healthcare provider, pharmacist, and patient knowledge expectations, and removal of (b) (4). The (b) (4) are to be removed from the assessment plan metrics, (b) (4)
9. The following heading for the Metric 10, Overall Assessment of REMS Effectiveness has been added.

Filspari REMS Assessment Plan

The revised REMS assessment plan must include, but is not limited to the following items. Additions are noted by underline and deletions are noted by ~~strikethrough~~.

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

(b) (4)

9 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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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
PDUFA Goal Date	February 17, 2023
OSE RCM #	2022-567
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
	Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	January 18, 2023
Subject	Evaluation of Proposed REMS
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics
Therapeutic Class	Endothelin and angiotensin receptor antagonist
Formulation(s)	200 mg and 400 mg oral film-coat tablet
Dosing Regimen	200 mg once daily for 14 days then increase to 400 mg once daily, as tolerated

Table of Contents

1. Introduction

This review evaluates the amendment to the proposed risk evaluation and mitigation strategy (REMS) submitted on December 19, 2022, for the new molecular entity (NME)[a] Filspari (sparsentan).[1] Travere Therapeutics (Travere) submitted a New Drug Application (NDA) 216403 for Filspari (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This application is under an accelerated approval review in the Division of Cardiology and Nephrology (DCN). The Applicant proposed a REMS to mitigate the risk of embryofetal toxicity due primarily to its mechanism of action as an endothelin receptor antagonist (ERA); sparsentan also blocks the angiotensin receptors (ARB). Current ERA products in the United States (US) for pulmonary arterial hypertension (PAH) are approved with a REMS to mitigate the risk of embryo-fetal toxicity and depending on the specific ERA drug, a REMS is also required to mitigate the risk of hepatotoxicity. During the review of the application, the Agency determined that there is potential hepatotoxicity risk with Filspari, and the Applicant was required to update their REMS to mitigate this risk. The Applicant amended their REMS proposal to include the additional risk of hepatotoxicity. The Applicant's proposed REMS is similar to the ERA REMS for PAH and consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of sparsentan outweigh the risk of embryo-fetal toxicity and hepatotoxicity.

The Applicant responded and accepted all the changes from the Agency's December 13, 2022 Information request[2] to:

1. Incorporate the revised REMS goals and objective statements and (b) (4) as provided.
2. Incorporate required monthly liver testing information throughout the REMS, and necessity to document negative pregnancy test result in the ***Patient Enrollment*** (b) (4) ***Form*** before prescribers can initiate Filspari for a patient.
3. Provide further clarification that patients in the inpatient setting may receive Filspari, provided that they are enrolled or will be enrolled prior to discharge, and how stakeholders are notified of their certification.
4. Provide details of what is included in the shipment file, and how often the daily files are reconciled to ensure compliance with the REMS.

The Applicant also provided post login screens to show the nonpublic accessible functionality of the REMS as an appendix in the REMS Supporting Document. Further, the Applicant incorporated edits such as renaming the (b) (4) to ***Patient Guide***, align changes in the REMS Document throughout the REMS, and provided general edits to correct page numbering in the REMS materials, remove redundancies, and improve readability.

However, further clarifications are needed on how the outpatient pharmacy captures the REMS requirements such as monthly counseling, completion of pregnancy and liver tests, authorization to dispense by prescribers when testing is not confirmed in the daily dispensing report and some of the

[a] Section 505-1(a) of the FD&C Act: *FDAAA factor (F):* Whether the drug is a new molecular entity

post login screens (i.e., Office Management Contact and REMS verification code) as this in unclear in the current proposal.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for sparsentan (NDA 216403) relevant to this review:

- 10/13/2022: Travere submitted a REMS amendment with a proposal to include the risk of hepatotoxicity.
- 12/13/2022: The Agency sent interim comments (ICs) #2 to the Applicant in response to their REMS amendment, dated October 13, 2022.
- 12/19/2022: Travere submitted a REMS amendment to NDA 216403 in response to the Agency's IC2 dated December 12, 2022.

3. Discussion

The Applicant submitted a REMS amendment on December 19, 2022 to update hepatotoxicity monitoring requirements and to incorporate changes provided in the Agency's ICs dated December 13, 2022. The Applicant provided further information of what is included in the daily dispensing report that is sent to the Filspari REMS. In addition, the Applicant provided post login screens to demonstrate the patient enrollment process, REMS verification processes, and stakeholder login functionalities.

However, further clarifications are needed for the REMS to be acceptable. The Applicant will need to:

1. Clarify the process of how safe use conditions including monthly counseling, pregnancy/ liver testing, and prescriber override authorization are captured and documented in the daily dispensing report sent to the REMS (e.g., pharmacist documents in an electronic file that is transmitted to the REMS or other methods).
2. Provide additional information on "Office Contact Management," as it is unclear what the roles and responsibilities of this stakeholder are.
3. Clarify if the inpatient pharmacy is required to obtain a verification code prior to dispensing in an inpatient setting as shown in the post login screens in REMS Supporting Document, Appendix 3. These new features are not described in the REMS Supporting Document and REMS materials.
4. Clarify how the pharmacist will be reminded to ensure safe use conditions are met in the REMS, and if the pharmacist will receive an alert to confirm safe use conditions are completed when obtaining a REMS verification code.
5. Add details on how the patient/guardian receives an email to sign and complete the attestation in the ***Patient Enrollment*** (b) (4) ***Form*** when not available to sign during the online enrollment to the REMS Supporting Document.

In addition, the Applicant will need to submit certifications of translation for the proposed ***Patient Enrollment*** (b) (4) ***Form*** and the ***Patient Guide*** to be provided in different languages (English,

Spanish, and Chinese). Lastly, additional edits are needed to remove (b) (4) incorporated within the inpatient pharmacy attestation section of the ***Inpatient Pharmacy Enrollment Form*** as they are not needed there.

4. Conclusions and Recommendation

DRM does not find the Filspari REMS as submitted on March 20, 2022, and amended on June 9, October 13, and December 19, 2022 to be acceptable. DRM recommends the comments in Section 5 be sent to the Applicant.

5. Comments for the Applicant

The following comments and attached redlined Filspari REMS materials are based on our review of the proposed REMS submitted by Travere on March 20 and amended June 9, October 13, December 12, and December 19, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment within 5 business days of receipt, by **January 26, 2023**. These comments should not be considered as the final edits to the REMS. The REMS Document and all REMS materials must align with the final approved labeling.

General comments:

We acknowledge that you have accepted all the changes noted in our December 12, 2022 interim comments. However, further clarifications and edits in the selected REMS materials are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions (PDF and Word versions) of the REMS materials should align.

As labeling negotiations are ongoing, language in the REMS may be subject to further changes to align with labeling.

REMS Document

The REMS Document is under review and not finalized. Further changes may be necessary to align with labeling.

REMS Supporting Document (RSD)

Clarify the following information in Appendix 3: Post Login Screens (PDF version):

1. Role and responsibility of the "Office Contact Management" personnel (pages 63-67/ 98). The "Office Contact Management" staff should not have the ability to assess required laboratory results or authorize refills of Filspari when required monitoring (pregnancy and liver enzyme tests) are not confirmed. Provide scenarios when the "Office Contact Management" personnel may act and not act on behalf of the prescriber. In addition, clarify if there is a limitation of how many staff can be designated as "Office Contact Management" designee by the certified prescriber. This information would need to be reflected in relevant REMS materials such as the

Prescriber and Pharmacy Guide and ***FAQs*** and may need to be accounted for in the Assessment Plan.

2. Purpose of the REMS verification code for the inpatient pharmacy (page 86-90/98). The REMS Document does not specify that the inpatient pharmacy must obtain an authorization to dispense before each dispense. If this is a requirement for inpatient pharmacies, it should be reflected in the REMS Document and affected REMS materials.

3. Whether the pharmacist will be reminded to ensure safe use conditions are met before obtaining a REMS verification code (pages 77-78/98) from the pharmacy portal of the REMS website. We encourage you to consider adding a reminder for the pharmacist to document completion of safe use conditions in the REMS verification process if it is currently not available. This information should also be reflected in the Pharmacy (outpatient and inpatient) sections of the REMS Supporting Document.

Include the following information in the REMS Supporting Document:

- Process of how safe use conditions including monthly counseling, pregnancy/ liver testing, and prescriber override authorization are captured and documented in the daily dispensing report sent to the REMS (e.g., pharmacist documents in an electronic file that is transmitted to the REMS or other methods).

- Process of how patients/legal guardian may receive an email to sign the patient attestation in the ***Patient Enrollment*** (b) (4) ***Form***, if the patient is not available to complete patient signature during online enrollment as shown in the PDF version of the RSD, Appendix 3: Post Log-in Screen (pages 85-90).

Ensure that the information in the Background Overview section (page 5) is updated to align with labeling.

Assessment Plan

- We will provide comments in a separate communication.

Inpatient Pharmacy Enrollment Form

- It is not necessary to include (b) (4) in the attestation statement as this is provided in other REMS materials. Remove this information (Section 3, Before dispensing, (b) (4)). See edits in redlined document.

REMS Website

- We acknowledge that you will be providing different languages (English, Spanish, and Chinese) for the ***Patient Enrollment*** (b) (4) ***Form*** and the ***Patient Guide***. Provide certifications of translation for these documents with your next REMS amendment or no later than 30 days after the REMS approval. This may be submitted as a REMS correspondence.

Submit a REMS amendment that includes revised REMS materials **within 5 business days by January 26, 2023**. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include the following:

	Materials	Required Formats
1	REMS Document	Clean MS Word, PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, PDF version
3	Prescriber Enrollment (b) (4) Form	Clean MS Word, PDF version
4	Patient Enrollment Form	Clean MS Word, PDF version
5	Outpatient Pharmacy Enrollment Form	Clean MS Word, PDF version
6	Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, PDF version
7	Prescriber and Pharmacy Guide	Clean MS Word, PDF version
8	(b) (4) Patient Guide	Clean MS Word, PDF version
9	Change in Reproductive Potential Status Form	Clean MS Word, PDF version
10.	REMS Website	Clean MS Word, PDF version
Other Materials		
11	Proprietary REMS website (appendix to REMS Supporting document)	Tracked MS Word, Clean MS Word, PDF version

6. Appendix

Enrollment Forms:

1. Inpatient Pharmacy Enrollment Form

7. References

1. Travere. Filspari NDA 216403, REMS amendment. December 19, 2022.
2. Park A. DRM. Information Request for NDA 216403. December 13, 2022.

2 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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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
PDUFA Goal Date	February 17, 2023
OSE RCM #	2022-567
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
	Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	December 12, 2022
Subject	Evaluation of Proposed REMS
Established Name	Sparsentan
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Name of Applicant	Travere Therapeutics
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2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for sparsentan (NDA 216403) relevant to this review:

- 10/13/2022: Travere submitted a REMS amendment to NDA 216403 to include risk mitigation strategies for hepatotoxicity in addition to embryo-fetal toxicity.
- 10/21/2022: The Agency issued a Review Extension for Major Amendment letter to Travere in response to the REMS amendment submitted to NDA 216403 on October 13, 2022.
- 11/14/2022: The Agency responded via email to Travere on the necessity for monthly liver testing instead of every (b) (4) liver testing, as proposed by Travere.
- 11/22/2022: Travere responded via email to the Agency's November 14, 2022 comments to require monthly liver testing in the Filspari REMS. In their response, Travere (b) (4) proposed monthly liver monitoring for the first year, and quarterly thereafter. Travere asserts that by the end of the first year (after approval), there will be sufficient data from the clinical trials available to further characterize the hepatotoxicity risk.

3. Discussion

[a] Section 505-1(a) of the FD&C Act: *FDAAA factor (F):* Whether the drug is a new molecular entity

The Applicant's proposed REMS requires additional changes to be acceptable.

During the course of the review of Filsapri, the review team proposed to include the risk of hepatotoxicity to the Filspari REMS. The risk mitigation strategies used in the Filspari REMS will be similar to the Bosentan REMS for both embryo-fetal toxicity and hepatotoxicity risks. Though the patient population in the chronic kidney disease program exposed to sparsentan was small and insufficient to provide clear characterization of the severity of hepatotoxicity, six cases were identified by the review team as probable or possible Drug-induced liver injury (DILI) with positive rechallenge results in most of these cases. In addition, the review team observed prolonged latency from drug initiation to the development of DILI (mean 200 days). No Hy's law cases were identified, however, there was one "near-miss" case for Hy's Law. The Division of Hepatology and Nutrition (DHN) review team recommended monthly monitoring and a post-market study to further characterize the risk of hepatotoxicity. The REMS Oversight Committee (ROC) was informed of the need to add the additional risk of hepatotoxicity in the Filspari REMS via a ROC email on September 27, 2022.[1] All ROC members concurred with including the risk of hepatotoxicity in the Filspari REMS. In addition, ROC members endorsed the review team's proposal for monthly liver testing (similar to Bosentan REMS). Travere was informed of this in the LCM package[2] and agreed in the LCM held on September 12, 2022 to submit a REMS amendment to mitigate the risk hepatotoxicity in the Filspari REMS.[3]

On October 13, 2022, Travere submitted an amendment to the Filspari REMS to incorporate the risk of hepatotoxicity and the Agency's comments and edits to the REMS proposal.[4] (b) (4) [redacted]. Given the number of probable cases of DILI, a "near- missed" Hy's Law case, positive rechallenges, prolonged latency in development of DILI, and the small population size exposed to sparsentan, the review team is concerned that prescribers in the postmarketing setting will not be familiar with the risk of hepatotoxicity and the need for close monitoring so that therapy may be stopped before incurring further liver injury. (b) (4) [redacted] monthly liver testing is necessary to ensure the benefits outweigh the risk of hepatotoxicity in patients who are administered sparsentan. This was communicated via email to the Applicant on November 14, 2022. However, Travere responded in an email dated November 22, 2022, (b) (4) [redacted], but proposed monthly monitoring for the first year, and quarterly thereafter to gather further data to characterize this risk with the completion of the phase 3 studies in the CKD program.[5] In a discussion with DRM, DCN, and DHN on December 7, 2022, the review team concurred with the Applicant's November 22, 2022 proposal for liver testing frequency. The monthly liver monitoring for the first year would be slightly below the observed maximum latency period to detect onset of DILI observed in the clinical trial, but it would likely capture most of the cases of DILI. We expect that prescriber training via product labeling and REMS would alert prescribers to closely monitor patients with elevations in liver enzymes or presenting with signs and symptoms of liver toxicity. In addition, required postmarket surveillance study and enhanced pharmacovigilance would help capture any potential DILI cases.

The review team also discussed further revisions to the REMS goal and objectives. Current Agency thinking is to align the REMS goal and objectives with key performance indicators (KPIs) to better reflect measurable outcomes so we may determine if the REMS is functioning as designed to achieve the goal of mitigating the risks of embryo-fetal toxicity and hepatotoxicity associated with Filspari. The targeted thresholds for the KPIs are based on the Agency's REMS experience with REMS designed to mitigate similar risks. The revised REMS objectives along with the targeted KPI thresholds will be communicated to the Applicant.

4. Conclusions and Recommendation

DRM does not find the Filspari REMS as submitted on March 20, 2022, and amended on June 9, 2022, and October 13, 2022, to be acceptable. DRM recommends the comments in Section 5 be sent to the Applicant.

5. Comments for the Applicant

The following comments and attached redlined Filspari REMS materials are based on our preliminary review of the proposed REMS submitted by Travere on March 20 and amended June 9, 2022, and October 13, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment within 5 business days of receipt, by **December 19, 2022**. These comments should not be considered as the final edits to the REMS. The REMS Document and all REMS materials must align with the final approved labeling.

General comments:

We concur with your 11/22/22 proposal to require monthly liver testing in the first year of Filspari treatment and quarterly thereafter. However, further changes are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions (PDF and Word versions) of the REMS materials should align.

- Update your REMS (REMS Document, REMS Supporting, REMS materials, and REMS website) to include the requirement of monthly liver testing in the first year, and quarterly thereafter.
- Ensure consistency of information throughout the REMS.
    - Align the information in the REMS Document with the REMS Supporting Document and REMS materials.
    - Update the inpatient pharmacy requirement throughout the REMS to include that Filspari may be dispensed to patients in an inpatient setting provided the patient is enrolled or will be enrolled prior to discharge. This is to ensure patient access and to prevent delays in sparsentan treatment while the patient is being enrolled in the Filspari REMS.
    - Align the page numberings in the MS Word and PDF versions of the REMS materials.
- Rename the "(b) (4)" to "Patient Guide" to align with current Agency thinking on the naming of REMS materials and to indicate the material's intended stakeholder in the first word of the title. Make sure to apply this title change throughout the REMS materials where the original naming, "(b) (4)" appears.

- Incorporate edits provided throughout the REMS materials to remove redundancies and clarify information.
- Revise all materials so that the font size is at least 10-point to improve material usability.
- Reformat text in all instances across all materials where a sentence is broken up across two pages.

As labeling negotiations are ongoing, language in the REMS may be subject to further changes to align with labeling.

REMS Document

Update and align the REMS materials and website with the changes in the REMS Document.

- REMS Goal:
  - We revised the REMS objectives to better reflect measurable outcomes. The REMS goal and objectives are revised as follows:

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

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

- REMS Requirements:
  - To prevent delays in treatment, inpatient pharmacies may dispense Filspari to patients, provided they are enrolled or are in the process of getting enrolled in the Filspari REMS during their inpatient stay. See redline edits in the inpatient pharmacy requirement section.

In addition, redlined edits and comments are provided throughout the REMS Document to improve information flow and to reduce redundancy.

REMS Supporting Document (RSD)

We acknowledge your response to provide non-public REMS website screenshots as an appendix to the RSD to allow for better understanding of the functionality of the REMS in a subsequent submission. We have the following comments to the RSD:

- Align all changes in the REMS Document to the REMS Supporting Document, specifically, the REMS goals/objectives and frequency of liver monitoring.
- Provide the following clarifications:
  - Define the method(s) in which prescribers and outpatient pharmacies are notified of their certification in the Filspari REMS (i.e., via email, text, call, or other communication methods).

- Describe what is included in the shipment file (including data for all dispenses of Filspari) that is submitted to the REMS daily (i.e., monthly counseling and confirmation of completion of pregnancy and liver testing).
- Clarify how often the REMS will monitor and reconcile the daily dispensing files/ product distribution data received daily from the outpatient pharmacies (i.e., daily, monthly, or other defined times).

- Incorporate edits provided to clarify that in the inpatient setting, patients may receive Filspari, provided the patient must be enrolled or will be enrolled prior to discharge.
- Your proposed targeted thresholds for key performance indicators (KPIs) to determine if the REMS is functioning as designed to achieve the goal of mitigating the risks of embryo-fetal toxicity and hepatotoxicity are too low. Based on experience with similarly designed REMS for similar risks, we are providing the following targeted KPI thresholds as starting points for the revised objectives:

Filspari REMS Objectives	KPIs
• Objective 1: Ensure that patients who can get pregnant are not pregnant before initiating Filspari	• KPI #1: (b) (4)% of all patients have documentation of negative pregnancy status prior to treatment initiation
• Objective 2: Minimize exposure in patients who may become pregnant while taking Filspari	• KPI #2: 98%* of all dispenses are associated with confirmation that pregnancy testing was performed, or prescriber authorized refill prior to each dispense
• Objective 3: Monitor for elevations in liver enzymes in patients exposed to Filspari	• KPI #3: 98%* of all dispenses are associated with confirmation that liver testing was performed, or prescriber authorized refill prior to each dispense
*For KPIs 2 and 3: (b) (4)	

- o (b) (4)

- Assessment Plan
  - We will provide comments in a separate communication.

Prescriber Enrollment (b) (4) Form

- Include documentation of a negative pregnancy test result prior to prescribing Filspari. See edits in redlined document.

Patient Enrollment (b) (4) Form

- In the Prescriber Authorization section of this form, reformat for clarity. Divide the section into two boxes (both still within section 4) to clearly differentiate selection between the reproductive status item and the liver testing item. A horizontal line needs to be added above the item that reads, “For this patient, have you reviewed the results of their current liver testing?”
- See comments provided in the redlined document to improve readability.

Outpatient Pharmacy Enrollment Form

- Incorporate edits to reinforce monthly counseling requirements in the redlined document.

Inpatient Pharmacy Enrollment Form

- Incorporate edits provided in the redlined document to clarify that the inpatient pharmacy may dispense Filspari to patients during their hospitalization provided these patients are enrolled or will be enrolled prior to discharge.

Prescriber and Pharmacy Guide

- Revise font color on the PDF version to a darker color, the current (b) (4) font provides poor readability. The numbers at the start of each section appear to be page numbers, not section numbers. Move the page numbers to the bottom of the page to avoid confusion. See redlined version for additional edits.

Patient Guide

- Revise font color on the PDF version to a darker color, the current (b) (4) font provides poor readability. The numbers at the start of each section appear to be page numbers, not section numbers. Move the page numbers to the bottom of the page instead to avoid confusion. See redlined version for additional edits.

Change in Reproductive Potential Status Form

- Incorporate edits provided in the redlined document for clarity and to ensure the MS Word and PDF versions align.

REMS Website

- We anticipate submission of your REMS website screenshots demonstrating the patient enrollment process, REMS verification and authorization processes, and stakeholder login functionalities in your next submission. Update the website to reflect all changes made within and across materials. The information in the REMS website should align with the REMS Document. See redlined version for additional edits.

Submit a REMS amendment that includes revised REMS materials **within 5 business days by December 19, 2022**. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include the following:

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7	Prescriber and Pharmacy Guide	Tracked MS Word, Clean MS Word, PDF version
8	(b) (4) Patient Guide	Tracked MS Word, Clean MS Word, PDF version
9	Change in Reproductive Potential Status Form	Tracked MS Word, Clean MS Word
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

6. Appendix

1. REMS Document

Training and Educational Materials:

2. Prescriber and Pharmacy Guide
3. (b) (4)

Enrollment Forms:

4. Prescriber Enrollment (b) (4) Form
5. Patient Enrollment Form
6. Outpatient Pharmacy Enrollment Form
7. Inpatient Enrollment Form

Patient Care Form:

8. Change in Reproductive Potential Status Form

Operations:

9. REMS website

7. References

1. Filspari (sparsentan) ROC by email, dated September 30, 2022.
2. Thereapeutics T. Late Cycle Meeting (LCM) Bacground Package - Sponsor Comments, September 8, 2022.
3. Park A. LCM minutes for Filspari (sparsentan) NDA 216403, dated October 12, 2022.
4. Travere. REMS amendment, dated October 13, 2022.
5. Travere. Response to Agency REMS Update (14 November 2022), dated November 29, 2022.

61 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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LAURA A ZENDEL
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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
PDUFA Goal Date	November 17, 2022
OSE RCM #	2022-567
Reviewer Name(s)	Theresa Ng, PharmD, BCPS, CDE
	Katherine Hyatt Hawkins Shaw, PhD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	September 23, 2022
Subject	Evaluation of Proposed REMS
Established Name	Sparsentan
Trade Name	Filspari
Name of Applicant	Travere Therapeutics
Therapeutic Class	Endothelin and angiotensin receptor antagonist
Formulation(s)	200 mg and 400 mg oral film-coat tablet
Dosing Regimen	200 mg once daily for 14 days then increase to 400 mg once daily, as tolerated

Table of Contents

1. Introduction

This review evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Filspari (sparsentan). Travere Therapeutics (Travere) submitted a New Drug Application (NDA) 216403 for Filsapri (sparsentan) with the proposed indication for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This application is under an accelerated approval review in the Division of Cardiology and Nephrology (DCN). The Applicant proposed a risk evaluation and mitigation strategy (REMS) to mitigate the risk of embryofetal toxicity due primarily to its mechanism of action as an endothelin receptor antagonist (ERA); sparsentan also blocks the angiotensin receptors (ARB).[1] Current ERA products in the United States (US) for pulmonary arterial hypertension (PAH) were approved with a REMS to mitigate the risk of embryo-fetal toxicity and depending on the specific ERA drug, a REMS was also required to mitigate the risk of hepatotoxicity. The Applicant's proposed REMS is similar to the ERA REMS for PAH and consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of sparsentan outweigh the risk of embryo-fetal toxicity.

2. Background

2.1. Regulatory History

The following is a summary of the regulatory history for NDA 216403 relevant to this review:

- 12/4/2020: A Type C meeting was held between the Agency and Applicant for sparsentan under IND 137918/ NDA 216403 for IgAN and IND (b) (4) for focal segmental glomerulosclerosis (FSGS), in which the Agency informed the Applicant that there is a risk of embryo-fetal toxicity with sparsentan, and other approved ERAs with a similar risk are subject to a REMS. The Agency informed the Applicant that at this time, we do not have sufficient information to determine whether a REMS will be necessary and if necessary, what the required REMS elements will be. The Agency asked that the Applicant provide a proposal to mitigate the potential risk of embryo-fetal toxicity for FDA to review.
- 1/11/2021: Sparsentan granted Orphan Drug Designation for the treatment of IgAN in the US.
- 5/14/2021: A Type B Pre-NDA meeting was held for sparsentan under IND (b) (4) for FSGS, in which the Agency informed the Applicant that a REMS will likely be necessary to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity.
- 3/20/2022: NDA 216403 submitted for the treatment of IgAN in adults aged 18 years and older.
- 5/11/2022: A Filing Communication Letter was issued to the Applicant to inform them that no filing issues were identified, and the application was granted priority review status. However, the letter indicated the proposed Filspari REMS was incomplete as only the PDF versions were submitted and both MS Word and PDF versions of the REMS are needed for review.
- 5/17/2022: The Agency issued an information request (IR) to the Applicant to submit both MS word and PDF versions of the proposed Filspari REMS for review.

- 6/9/2022: The Applicant submitted an amendment to the application with the MS word and pdf versions of the proposed REMS.
- 6/28/2022: The Agency held a Mid-Cycle meeting (MCM) with the Applicant via teleconference. The Agency informed the Applicant that we agreed with the necessity for a REMS to mitigate the risk of embryo-fetal toxicity. The Applicant was also informed that an imbalance in hepatotoxicity events is under review, and they should review how other ERAs mitigate this risk.
- 9/1/2022: Late Cycle meeting background package sent to the Applicant informing them of the Agency's determination that drug induced liver injury (DILI) is a potential risk for sparsentan. The Applicant was informed of the need to describe this risk in labeling and submit an amendment to the proposed REMS to include a goal, elements to assure safe use (e.g., monthly liver testing), and an implementation system to prevent hepatotoxicity. Additional postmarketing requirements may be required. Further, to align with the Department of Health and Human Services (HHS) 2020 and 2023 initiatives to achieve health equality, eliminate disparities and improve health in all groups, the Agency requested the incorporation of gender-neutral language, using categories based on whether a patient can or cannot become pregnant, for newly established REMS for embryo-fetal toxicity. The Applicant was also informed that labeling would need to align with the gender-neutral language in the REMS.
- 9/12/2022: The Agency held a Late cycle teleconference with the Applicant. The Agency re-affirmed the necessity of a REMS to mitigate the risk of hepatotoxicity. The Applicant is to submit an amendment to the proposed REMS.

3. Discussion

The Applicant's proposed REMS requires additional changes to be acceptable.

On August 1, 2022, a meeting of the REMS Oversight committee (ROC) was convened to discuss the need for a REMS for sparsentan to mitigate the risk of embryo-fetal toxicity. The ROC concurred with the necessity of a REMS with elements to ensure safe use (ETASU) to mitigate the risk of embryo-fetal toxicity.[2] The ROC agreed with the review team's recommended changes to the Applicant's proposed REMS. These changes included:

- Having the pharmacist verify pregnancy testing is completed prior to dispensing (b) (4)
- Having the prescriber (b) (4) report misclassifications of a female patient's reproductive status to the REMS
- Limiting dispenses to 30-days (b) (4) to ensure pregnancy testing is completed prior to dispensing

In addition, the ROC endorsed the use of gender-neutral language in the Filspari REMS as this aligns with one of the health priorities in the Healthy People 2020 and 2023 initiatives to achieve health equality, eliminate disparities and improve health in all groups. Using risk categories based on whether a patient can or cannot become pregnant would alleviate the access burden on transgender patients by avoiding

the unnecessary identification with a particular gender. The Applicant agreed to incorporate gender-neutral language in the REMS and labeling in their response the LCM meeting package.[3]

Hepatotoxicity was identified as a risk associated with sparsentan that the Applicant did not fully address in their proposed labeling and REMS. DCN consulted the Division of Hepatology and Nutrition (DHN) to evaluate the potential risk of DILI in the clinical development program for rare chronic kidney diseases (which included IgAN and FSGS). DHN shared their findings with the review team in an internal late cycle meeting on August 31, 2022.[4] Though no Hy's Law or jaundice cases were identified, an imbalance of Temple's Corollary at elevated aminotransferase (AT) > 5 times upper limit of normal (ULN) consistent with potential for increased hepatocellular injury was observed in subjects treated with sparsentan. DHN reviewed 5 cases (four probable and one possible) of potential DILI in the IgAN pivotal phase 3 trial (PROTECT) and 1 probable case in DUPLEX, a phase 3 trial for FSGS. Three of the four probable DILI cases in PROTECT had positive rechallenges (elevations of liver enzymes when sparsentan was re-initiated) with hepatocellular injuries which were mostly modest and resolved when sparsentan was held. In DUPLEX, the one probable case was positive on rechallenge followed by development of tolerance. However, the number of patients with chronic kidney disease exposed to sparsentan in the clinical development program is limited (only 500 patients), and well below the desired threshold of a few thousand which provides a 95% chance of detecting a 1 in 1000 risk of a Hy's Law case. In addition, latency was unusually long for the probable and possible cases (mean 200 days, range 28-406 days). The DHN reviewer concluded that drug-induced liver injury is a potential risk of sparsentan, and Hy's Law events may occur with greater exposure in the postmarketing population. DHN recommended monthly monitoring of liver tests, for at least 12 to 14 months, to mitigate the risk of hepatotoxicity if sparsentan is approved. Based on DHN's analysis and other considerations including potential drug-drug interactions due to sparsentan's CYP3A4 metabolism and inhibitor activities, the limited size of the safety database, prescriber population that may not be familiar with monitoring for hepatotoxicity, and the known risk of hepatotoxicity in the ERA drug-class, DCN and DRM agree that hepatotoxicity should be included in the REMS. Specific monitoring and follow-up requirements are still under review. The Applicant was informed in the late cycle meeting package of the Agency's determination that DILI is a potential risk and a REMS would be necessary to ensure the benefits outweigh the risk of hepatotoxicity associated with sparsentan.[5] This was re-affirmed in the LCM teleconference with the Applicant.

4. Conclusions and Recommendation

DRM does not find the Filspari REMS as proposed to be acceptable. DRM recommends the comments in Section 5 be sent to the Applicant.

5. Comments for the Applicant

The following comments and attached redlined Filspari REMS materials are based on our preliminary review of the proposed REMS submitted by Travere on March 20 and amended June 9, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment within 15 business days of receipt. These comments should not be considered as the

final edits to the REMS. The REMS Document and all REMS materials must align with the final approved labeling.

General comments and information requests:

Further changes are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions of the materials should be aligned (PDF and Word versions).

- Update the REMS to include safe-use conditions and stakeholder requirements to mitigate the risk of hepatotoxicity in addition to the risk of embryo-fetal toxicity.
- The Agency is moving toward establishing REMS goals based on Public Health Preventive Aims (Adopted from: *World Health Organization*, *Centers for Disease Control*). We have provided an updated Filspari REMS goal based on this. See the redlined REMS Document for the revised goal and update your REMS proposal accordingly.
- The Agency is incorporating gender-neutral language in newly established REMS for embryo-fetal toxicity to achieve health equality, eliminate disparities and improve health in all groups as one of the health priorities in the Healthy People 2020 and 2023 initiatives. As communicated in the Late-Cycle Meeting package, update the language in the REMS Document and all REMS materials to establish gender neutral patient categories. The language used in the REMS should also align with labeling to include gender-neutral language. You may refer to other REMS, such as isotretinoin (iPLEDGE) and Qsymia for examples.
- (b) (4)
- Bold the titles of all REMS materials (e.g., Patient Enrollment (b) (4) Form, (b) (4) , and Prescriber and Pharmacy Guide) when they are mentioned in the REMS Document and REMS materials to distinguish them from the rest of the text.
- Remove "(b) (4)" after REMS (e.g., REMS (b) (4)) throughout the REMS materials as it is repetitive and not necessary.
- Use the term "prescriber" instead of "(b) (4)" throughout the REMS as nurse practitioners and physician assistants may also prescribe.
- Align all REMS materials and the REMS Supporting Document with edits made to the REMS Document. All REMS information and operations must reflect what is in the REMS Document.
- Align the attestation statements to the stakeholder requirements in the REMS Document for all the stakeholder enrollment forms.

REMS Document

Redlined edits and comments are provided. Please update and align the REMS materials and website with the changes in the REMS Document.

- REMS Goal:
  - Update the REMS goal statement to align with the Public Health Preventive Aims provided.
- Stakeholder enrollment/ certification:

    - Clarify why outpatient pharmacies have only one option to enroll (by fax) whereas inpatient pharmacies may enroll by fax and online.
- REMS Requirements:
    - [redacted] (b) (4) Align the pharmacy requirement with current ERA REMS for pulmonary arterial hypertension (PAH) which requires prescribers to assess monthly pregnancy test results of patients while pharmacists verify that pregnancy testing is completed prior to dispensing.
    - We do not agree with [redacted] (b) (4) The proposed Filspari REMS [redacted] (b) (4) requires the prescriber to report misclassifications to the REMS via the *Change in Reproductive Potential Status Form*. The pharmacist should continue to verify that reproductive status has not changed for a patient prior to dispensing.
    - We do not agree with [redacted] (b) (4) . To align with the approved ERA REMS, prescribers should order and assess monthly pregnancy test results.
- Dispensing:
    - We do not agree with [redacted] (b) (4) . Consistent with the ERA REMS, the pharmacy may dispense up to a 30-day supply to ensure safe-use conditions (i.e., pregnancy testing is completed, counseling is provided on the risk of embryo-fetal toxicity and hepatotoxicity) are met prior to dispensing
- Edits to ensure consistency include:
    - Information that the drug is only available through a restricted distribution program.
    - Pregnancy testing one month after discontinuation of treatment.

REMS Supporting Document (RSD)

- Align all changes in the REMS Document to the REMS Supporting Document.
- Consider adding non-public REMS website screenshots as an appendix to the RSD to allow for better understanding of the functionality of the REMS. (See comments on the REMS website below.)
- Provide information on the verification process that the outpatient pharmacy undertakes to ensure all REMS requirements (i.e., prescriber certification, patient enrollment, routine pregnancy and liver testing, and monthly counseling) are met prior to dispensing.
    - Clarify how the REMS captures and records the data as required by the REMS.
    - Provide information on verification method(s) the REMS will employ to ensure the REMS requirements are met (i.e., authorization to dispense from the REMS or REMS Coordinating Center) prior to dispensing.
    - Clarify how often (such as daily, weekly, or other defined frequency) the outpatient pharmacy is required to report shipment files to the REMS.
- Clarify how pharmacies are notified of a patient's reproductive status change by the REMS.

- Clarify the scenarios of “insurance needs” and “prescriber authorization” with regard to your proposal to allow the prescriber to grant a one-time authorization to dispense Sparsentan when the patient has not completed a pregnancy test or requests a greater than 30-day supply.
- Clarify the process of how a prescriber will follow-up with a patient to ensure REMS requirements are implemented when a patient’s reproductive status changes from non-reproductive potential to reproductive potential.
- Provide hours of operation of the REMS Coordinating Center.
- To align with the REMS website:
    - Include information on how prescribers and pharmacies would create an account to access the REMS website and conduct stakeholder activities.
    - Add detail on what happens after an inpatient pharmacy is certified (i.e., added to the REMS database, create login to access the REMS).
- Propose key performance indicators (KPIs) to determine if the REMS is functioning as designed to achieve the goal of mitigating the risks of embryo-fetal toxicity and hepatotoxicity.
- Assessment Plan
    - Update the Assessment Plan to include the risk of hepatotoxicity.
    - We will provide comments after reviewing the revised Assessment Plan.

Prescriber Enrollment (b) (4) Form

- Include fields for contact information (i.e., address, phone#, fax #) for both primary and secondary offices, as they may be different than the prescriber information.
    - See edits in redlined document regarding pregnancy monitoring by prescribers.

Patient Enrollment (b) (4) Form

- Update the pregnancy testing requirements ordered by prescribers and update the requirement to include pregnancy testing one month after discontinuing treatment.

Outpatient Pharmacy Enrollment Form

- Include a field for the credential of the authorized representative for the pharmacy.
- See edits and formatting changes in the redlined document.

Inpatient Pharmacy Enrollment Form

- See edits provided in the redlined document.

Prescriber and Pharmacy Guide

- Update the goals, objectives, and requirements to align with the REMS Document.
- Add the following to the overview section to align with the information in the REMS Document:
    - Prescribers must report any change or misclassification in a patient’s reproductive potential status in the PROPRIETARY NAME REMS
    - Prescribers must report any pregnancies that occur during treatment or within one month after discontinuation of PROPRIETARY NAME to the PROPRIETARY NAME REMS
    - See edits and formatting changes in redlined document

(b) (4)

- See edits to redlined document to better reflect the flow of information and to align with the REMS Document.

Change in Reproductive Potential Status Form

- Include fields in the prescriber information section to collect contact information (address, city, state, zip code phone number, fax number, email address) to allow for follow-up with the prescriber if needed by the REMS Coordinating Center.
- See edits provided in the redlined document.

REMS Website

To allow the Agency better understanding of the functionality of the REMS, include REMS website screenshots including the operational processes involved after stakeholder log-in to the REMS website and verification processes. We understand that there may be proprietary information related to REMS operations that may not be appropriate for public access in the REMS website. Proprietary information may be included as an appendix to the REMS Supporting Document.

- Align changes to the REMS Document to the REMS Website.
- Include the hours of operation for the REMS Coordinating Center in the relevant REMS materials and REMS Supporting Document.
- To align with information from the REMS Supporting Document, provide screenshots to show the functionality of the following:
    - Login screenshots for prescribers and pharmacies.
    - Patient enrollment process, including documentation that once enrolled, the patient will be assigned a unique patient identification number
    - Outpatient pharmacy enrollment process
    - Verification process that outpatient pharmacies undergo to ensure REMS requirements are met prior to dispensing
    - When a prescriber grants a one-time authorization to dispense greater than a 30-day supply to the patient
    - How a pharmacist records verification of completion of pregnancy/ liver tests and monthly counseling in the REMS and how the REMS authorizes dispensing after verifying that all requirements are met.
- See editorial changes in the redlined REMS website screenshots.

Submit a REMS amendment that includes revised REMS materials within 15 business days. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include the following:

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7. References

1. Thereapeutics T. Risk Evaluation and Mitigation Strategy for Filspari NDA 216403, March 20, 2022.
2. REMS Oversight Committee (ROC) Meeting Minutes, August 31, 2022.
3. Thereapeutics T. Late Cycle Meeting (LCM) Bacground Package - Sponsor Comments, September 8, 2022.
4. Hayashi P. DHN. Drug-Induced Liver Injury Review for Sparsentan, September 20, 2022.
5. Park A. FDA. Late-Cycle Meeting Package- Background Package, September 1, 2022.

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