FILSPARI® (sparsentan)
Prescribing Information Update

Summary

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[1]
- On September 5, 2024, FILSPARI was granted full approval by the FDA[2]
- Approval was based on 2-year confirmatory data from the PROTECT study, primarily based on mean eGFR slope[2]

Background

- The effect of FILSPARI on proteinuria (UPCR) and kidney function (eGFR) was assessed in a randomized, double-blind, active-controlled, global study in adult patients with primary IgAN[1]
- Statistical analyses for full approval involved an FDA-preferred approach which imputed missing patient data throughout all phases of the study[3]

Study Data

- The PROTECT trial met the primary endpoint of relative change from baseline in UPCR at Week 36. FILSPARI-treated patients showed a 45% decrease in UPCR compared to a 15% decrease in irbesartan-treated patients[1,3]
- Analysis of all study patients (N=404) found treatment effects in UPCR at Week 36 and Week 110 were consistent with the interim analysis[1]
- Rate of kidney function decline was significantly decreased in FILSPARI-treated patients. Mean eGFR slope from baseline to Week 110 was −3.0 vs −4.2 mL/min/1.73 m^2 in FILSPARI and irbesartan patients, respectively (P=0.0168)[1]

Prescribing Information

FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.[1] Full approval was granted by the FDA on September 5, 2024, based on updated data of mean eGFR slope results in the PROTECT study.[2]

Detailed revisions to the Prescribing Information are presented in **Table 1**.

Table 1. Itemized Changes in the FILSPARI Prescribing Information

Section	Former Statement	Updated Statement
Indication and Usage (p1, 4)	FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g. This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.	FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.
Dosage and Administration (p1)	Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily.	Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to 400 mg once daily, as tolerated. When resuming FILSPARI after an interruption, consider re-titration.
Contraindications (p1, 6)	• Pregnancy • Do not coadminister FILSPARI with angiotensin receptor blockers, endothelin receptor antagonists, or aliskiren	• Pregnancy • Concomitant use with angiotensin receptor blockers (ARBs), ERAs, or aliskiren
Warnings and Precautions (p1)	• Hepatotoxicity • Embryo-fetal toxicity • Hypotension • Acute kidney injury • Hyperkalemia • Fluid retention	• Hypotension • Acute kidney injury • Hyperkalemia • Fluid retention
Adverse Reactions (p1)	Most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.	Most common adverse reactions (≥5%) are hyperkalemia, hypotension (including orthostatic hypotension), peripheral edema, dizziness, anemia, and acute kidney injury.
Drug Interactions (p1)	CYP2B6, 2C9, and 2C19 substrates: Monitor for efficacy of the concurrently administered substrates. Decreased exposure of these substrates.	CYP2B6, 2C9, and 2C19 substrates: Monitor for substrate efficacy. Decreased exposure of these substrates.
Black Box Warning, Hepatotoxicity (p3)	In clinical studies, elevations in ALT or AST of ≥3 times the ULN have been observed in up to 2.5% of FILSPARI-treated patients…	In clinical studies, elevations in ALT or AST of ≥3 times the ULN have been observed in up to 3.5% of FILSPARI-treated patients…
Section 2.1, General Consideration (p4)	Prior to initiating treatment with FILSPARI, discontinue use of RAAS inhibitors, ERAs, and aliskiren.	Prior to initiating treatment with FILSPARI, discontinue use of RAAS inhibitors and ERAs.

Section 5.1, Hepatotoxicity (p6)	Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.	Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 3.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.
Section 6.1, Clinical Trials Experience (p8-9)	The data below reflect FILSPARI exposure in 202 patients with a median duration of 73 weeks (up to 110 weeks).	The data below reflect FILSPARI exposure in 202 patients with a median duration of 110 weeks.
Section 6.1, Clinical Trials, Laboratory Tests (p9)	The incidence of hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (11%) compared to the irbesartan arm (5%).	The incidence of hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (19%) compared to the irbesartan arm (13%).
Section 12.3, Pharmacokinetics (p14)	Following a single oral dose of 400 mg sparsentan, the mean Cmax and AUC are 6.97 µg/mL and 83 µg×h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean Cmax and AUC are 6.47 µg/mL and 63.6 µg×h/mL, respectively.	Following a single oral dose of 400 mg sparsentan, the mean Cmax and AUC are 7.0 µg/mL and 83 µg×h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean Cmax and AUC are 6.5 µg/mL and 63.6 µgxh/mL, respectively.
Section 14, Clinical Studies (p17)	The effect of FILSPARI on proteinuria was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT, NCT03762850) in adults with biopsy-proven primary IgAN, eGFR ≥30 mL/min/1.73 m2, and total urine protein ≥1.0 g/day on a maximized stable dose of RAS inhibitor treatment that was at least 50% of maximum labeled dose. Patients with other glomerulopathies or those who had been recently treated with systemic immunosuppressants were excluded.	The effect of FILSPARI on proteinuria and kidney function (estimated glomerular filtration rate, eGFR) was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT, NCT03762850) in adults with biopsy-proven primary IgAN, eGFR ≥30 mL/min/1.73 m2, and total urine protein ≥1.0 g/day on a stable dose of maximally-tolerated RAS inhibitor treatment. Patients with chronic kidney disease due to another condition in addition to IgAN or those who had been recently treated with systemic immunosuppressants were excluded.
Section 14, Clinical Studies (p17)	Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial, but use of SGLT2 inhibitors was prohibited.	Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial. Concomitant use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, other RAS inhibitors, and aldosterone blockers were prohibited.
Section 14, Clinical Studies (p17)	The 281 patients who reached Week 36 had a mean age of 46 years (range 18 to 76 years); 69% were male, 62% White, 35% Asian, and 1% Black or African American. Approximately 77% had a history of hypertension, 12% diabetes or impaired fasting glucose, and 53% hematuria. Mean (SD) baseline eGFR was 56 (24) mL/min/1.73 m2.	The 404 patients who enrolled and received study medication had a mean age of 46 years (range 18 to 76 years); 70% were male, 67% White, 28% Asian, and 1% Black or African American. Approximately 78% had a history of hypertension, 11% had diabetes or impaired fasting glucose, and 56% had hematuria based on urine dipstick. At baseline the mean eGFR was 57 mL/min/1.73 m2, the geometric mean UPCR was 1.2 g/g, and 49 (12%) patients had proteinuria >3.5 g/24 hours.
Section 14, Clinical Studies (p17)	The primary endpoint was the relative change from baseline in UPCR at Week 36.	The primary efficacy endpoint for the interim analysis was the change from baseline in urine protein/creatinine ratio (UPCR) at Week 36 based on the first 281 randomized patients who had reached the Week 36 visit. The key

		secondary efficacy endpoint for the final analysis was the rate of change in eGFR over a 110-week period following initiation of randomized therapy.

In addition to the edits described in Table 1, the FILSPARI Prescribing Information includes updated efficacy and safety data.

For more information, please refer to the attached Prescribing Information.

Background

The PROTECT Study

The effect of FILSPARI on proteinuria and kidney function (eGFR) was evaluated in the PROTECT study (NCT03762850), a phase 3, global, randomized, multicenter, double-blind, active-controlled global study in adults with biopsy-proven primary IgA nephropathy, eGFR ≥30 mL/min/1.73 m^2, and total urine protein ≥1 g/day, while taking stable doses of maximally-tolerated RAS inhibitor therapy. The study excluded patients with chronic kidney disease due to other conditions in addition to IgA nephropathy and patients recently treated with systemic immunosuppressive therapies. Patients were randomized 1:1 to either FILSPARI 200 mg/day or irbesartan 150 mg/day for 14 days. Patients in the FILSPARI group were subsequently titrated to 400 mg/day, and irbesartan patients to 300 mg/day. SGLT2 inhibitors, other RAS inhibitors, and aldosterone blockers were prohibited throughout the study. Rescue immunosuppressive therapy could be utilized at the discretion of the investigator.[1]

The primary efficacy endpoint for the interim analysis was change in UPCR at Week 36 from baseline for the first 281 patients to reach Week 36. The key secondary efficacy endpoint in the final analysis was rate of change in eGFR following the initiation of randomized treatment over 110-weeks.[1]

Final analysis of the PROTECT data utilized an imputation method preferred by the FDA using the ITT population, in which missing data were imputed for subjects throughout the entire study who prematurely discontinued treatment, utilized IST or RRT, or died. This imputation method assumed missing data were not at random, which differs from the previous prespecified primary analysis which assumed that data were missing at random. The prespecified analysis also used results obtained only during the double-blind treatment phase. In this original analysis, data were imputed for patients once they completed the blinded treatment and included data after patients had received rescue therapy. This resulted in a nonsignificant trend in the total eGFR slope in favor of sparsentan.[3]

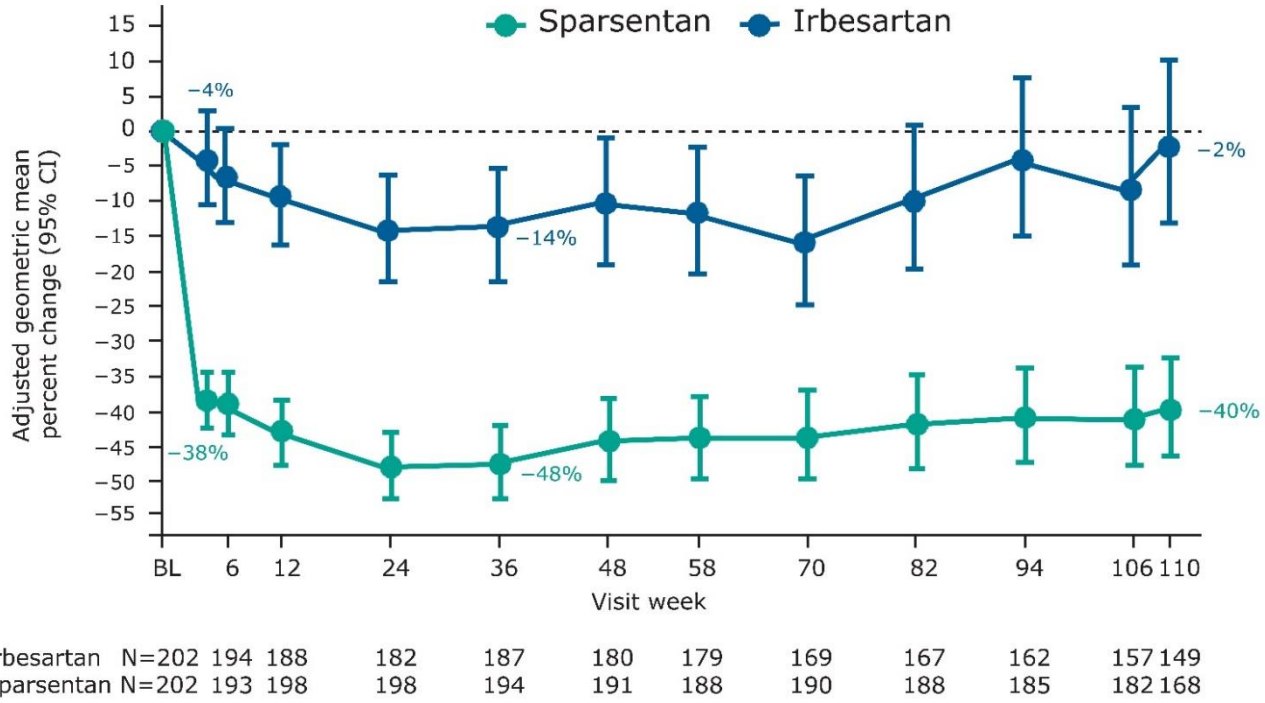
Study Data

The FDA-preferred imputation analysis further clarified results across UPCR and eGFR endpoints described in previous publications and the Prescribing Information.

UPCR

The ITT analysis of 281 patients who reached Week 36 demonstrated that the PROTECT trial met the primary endpoint of relative change from baseline in UPCR at Week 36. FILSPARI-treated patients showed a 45% decrease in UPCR relative to baseline vs a 15% decrease in irbesartan-treated patients, resulting in a 35% reduction in the ratio of mean UPCR (95% CI, 23% to 45% reduction; *P*<0.0001). Final analysis of all patients (N=404) found that treatment effects in UPCR at Week 36 and Week 110 were consistent with findings from the interim analysis. Mean percent change from baseline through the double-blind period is presented in **Figure 1**.[1,3]

Figure 1. Geometric Mean Percent Change from Baseline in UPCR Ratio Through Week 110 (PROTECT, FAS)



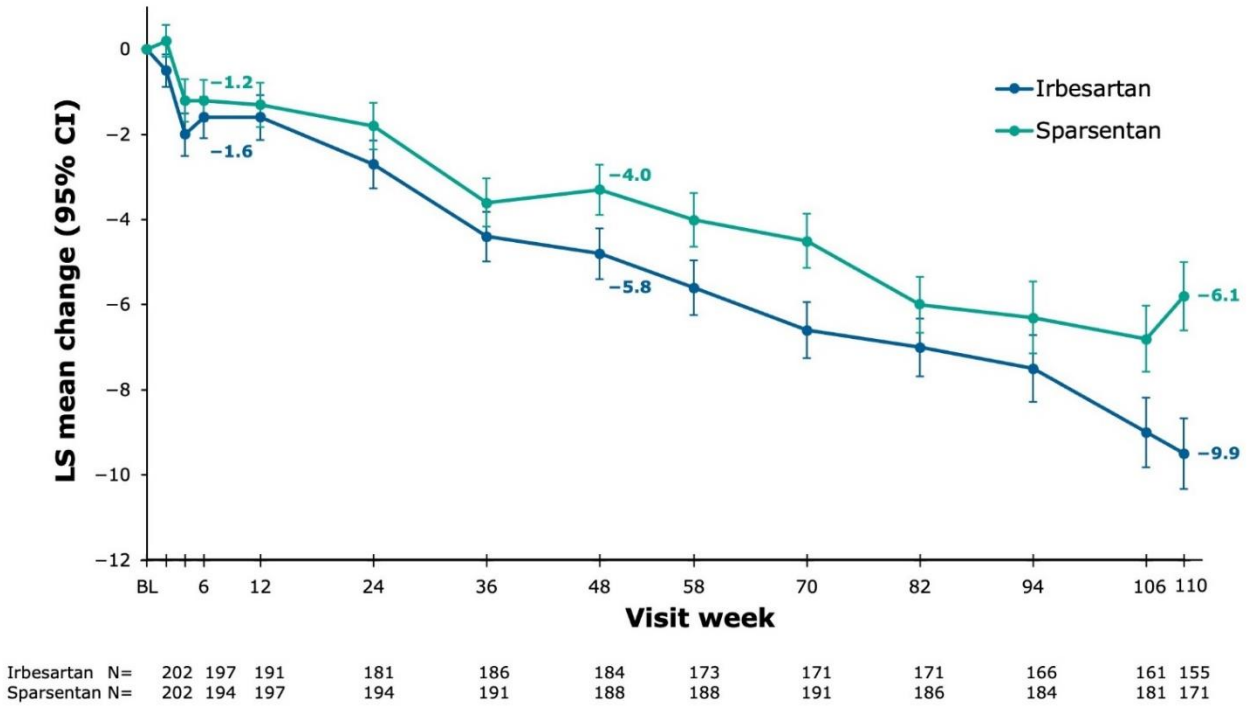
Adjusted GMPC of UPCR was based on MMRM stratified by screening eGFR and total urine protein excretion. MMRM analysis includes UPCR data during the double-blind period up to week 110 regardless of treatment discontinuation or immunosuppressive therapy initiation. Missing data were imputed using multiple imputation under assumptions of missing at random and missing not at random depending on the patient's intercurrent event status. Baseline was defined as the last non-missing observation on or prior to the start of dosing. Counts in axis table represent number of subjects with observed UPCR data by visit and treatment group.

eGFR

Compared to irbesartan, FILSPARI significantly reduced the rate of decline of kidney function. Mean eGFR slope from baseline to Week 110 was −3.0 mL/min/1.73 m^2 per year in FILSPARI-treated patients vs −4.2 mL/min/1.73 m^2 per year in patients treated with irbesartan. This reflects a treatment effect of 1.2 mL/min/1.73 m^2 per year (95% CI, 0.2 to 2.1; *P*=0.0168). The treatment effect was consistent across demographic and baseline disease-state subgroups. The treatment effect was not observed in a small number of study patients with an eGFR ≥90 mL/min/1.73 m^2.[1]

Mean change in eGFR from baseline through the double-blind treatment phase is described in **Figure 2**.[1]

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



eGFR was calculated using the CKD-EPI equation. Baseline was defined as the last non-missing observation on or prior to the start of dosing. The analysis includes eGFR data during the double-blind period up to Week 110 regardless of treatment discontinuation or immunosuppressive therapy initiation. Rescue immunosuppressive treatment for IgAN was initiated in 7 (3%) and 18 (9%) patients in the FILSPARI and irbesartan group respectively.

Current and previous PROTECT endpoint data are summarized in **Table 2**.[3]

Table 2. Comparison of Endpoint Results in the PROTECT Study

Endpoint	Previously Published PROTECT Results (95% CI)	Imputation Method PROTECT Results (95% CI)[a,b]
Chronic slope (primary)	Spar: -2.7 (-3.4, -2.1) Irb: -3.8 (-4.6,-3.1) Diff: 1.1 (0.1, 2.1) [*P*=0.037]	Spar: -2.9 (-3.6, -2.2) Irb: -4.2 (-4.9, -3.5) Diff: 1.3 (0.3, 2.3) [*P*=0.0087]
Total slope (primary)	Spar: -2.9 (-3.6, -2.2) Irb: -3.9 (-4.6, -3.1) Diff: 1.0 (-0.03, 1.94) [*P*=0.058]	Spar: -3.0 (-3.7, -2.4) Irb: -4.2 (-4.9, -3.5) Diff: 1.2 (0.2, 2.1) [*P*=0.0168]
eGFR change from BL to Week 6	Spar: -1.2 (-2.2, -0.3) Irb: -1.6 (-2.6, -0.7) Diff: 0.4 (-1.0, 1.7)	Spar: -1.2 (-2.2, -0.3) Irb: -1.6 (-2.6, -0.7) Diff: 0.4 (-0.9, 1.8)
eGFR change from BL to Week 110	Spar: -5.8 (-7.4, -4.2) Irb: -9.5 (-11.2, -7.9) Diff: 3.7 (1.5, 6.0)	Spar: -6.1 (-7.7, -4.4) Irb: -9.9 (-11.5,-8.3) Diff: 3.8 (1.6, 6.1)
UPCR percent change from BL to Week 110	Spar: -42.8 (-49.8, -35.0) Irb: -4.4 (-15.8, 7.9) Ratio: 0.60 (0.50, 0.72)	Spar: -39.8 (-46.6, -32.1) Irb: -2.4 (-13.6, 10.3) Ratio: 0.62 (0.52, 0.73) [*P*<0.0001]

[a]One hundred imputed datasets are created by assuming Missing at Random to create monotone missing pattern for all subjects, followed by multiple imputation procedure under the assumption of Missing at Random for subjects without intercurrent event of premature treatment discontinuation, new use of any systemic immunosuppressive therapy for renal indication, RRT, or death; jump to reference imputation for subjects with intercurrent event of premature treatment discontinuation or new use of any systemic immunosuppressive therapy and without RRT or death; and by drawing from observed eGFR values less than or equal to the 1st percentile for subjects with RRT or death.
[b]For Lancet and label, CIs were typically double rounded. That practice is continued here.

Safety

FILSPARI was generally well tolerated in clinical trials. AEs reported in ≥2% of patients in the previous and current Prescribing Information are presented in **Table 3**.[1]

Table 3. AEs Reported at Median 110 Weeks of Treatment in Revised Prescribing Information

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

[a]Includes related terms.
[b]Elevations in ALT or AST >3-fold ULN.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine transaminase; ARB, angiotensin-receptor blocker; AST, aspartate transaminase; AUC, area under the concentration-time curve; BL, baseline; CI, confidence interval; CKD-EPI, Chronic Kidney Epidemiology Collaboration; C_{max}, maximum serum concentration; DBP, diastolic blood pressure; Diff, difference; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; FAS, full analysis set; FDA, US Food and Drug Administration; GMPC, geometric mean percent change; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; Irb, irbesartan; IST, immunosuppressive therapy; ITT, intention-to-treat; KF, kidney failure; KRT, kidney replacement therapy; MMRM, mixed-model repeated measures; N, number of subjects with available data at time of analysis; RAAS, renin-angiotensin-aldosterone system; RRT, renal replacement therapy; SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; Spar, sparsentan; TEAE, treatment-emergent adverse event; UACR, urine albumin-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-creatinine ratio.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; September 2024.
2. Travere Therapeutics announces full FDA approval of FILSPARI® (sparsentan). Press Release. September 5, 2024. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-full-fda-approval-filsparir
3. Data on file. Travere Therapeutics Inc; 2024.