FILSPARI® (sparsentan)
Use With Diuretics

Summary

Prescribing Information

- FILSPARI is 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[1]
- Fluid retention may occur with ERAs, and has been observed in clinical studies with FILSPARI[1]

Background

- Sparsentan is an investigational therapeutic candidate for the treatment of FSGS[4,5]

Study Data

The PROTECT Study

- Patients with edema were allowed to discontinue, pause and restart, or decrease the dose of study treatment while remaining in the study[6]
- Potassium-sparing diuretics were not to be coadministered with sparsentan in the PROTECT study; the protocol made allowances for treatment of patients with worsening edema, including use of other diuretics[6-8]
- Diuretic use initiated on or after beginning study drug was reported in 49 (24%) sparsentan patients and 54 (27%) irbesartan patients[9]

The DUET Study

- During the 8-week double-blind period, 6.8% of patients in the sparsentan group were on a thiazide diuretic and 35.6% were on a loop diuretic. In the irbesartan group, 16.7% of patients were on a thiazide diuretic and 22.2% were on a loop diuretic[4]
- After 8 weeks of treatment, there were no meaningful between-group differences in overall use and changes in diuretic treatment, or in severity of edema[4]
- A higher incidence of peripheral edema was reported in patients taking sparsentan (12.3%) compared to those on irbesartan (2.8%)[4]

The DUPLEX Study

- At baseline, 68 (37%) patients in the sparsentan group and 73 (39%) patients in the irbesartan group were taking diuretic medication[10]

- Throughout the study, 106 (57.6%) sparsentan-treated patients and 102 (54.5%) patients taking irbesartan utilized diuretic therapy[10]

Prescribing Information

Hyperkalemia

Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease or taking concomitant potassium-increasing drugs (eg, potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.[1]

Fluid Retention

Fluid retention may occur with endothelin receptor antagonists and has been observed in clinical studies with FILSPARI. FILSPARI has not been evaluated in patients with heart failure.

If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.[1]

NSAIDs, Including Selective COX-2 Inhibitors

Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure. These effects are usually reversible.[1]

Agents Increasing Serum Potassium

Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.[1]

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

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[11-13]

The PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan compared to 300 mg of irbesartan.[14] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. Patients with urine protein ≥1 g/day at screening, eGFR ≥30 mL/min/1.73 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[6] The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[6,15] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (urinary protein excretion <0.3 g/day) and partial (urinary protein excretion <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[8] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[8,16]

The DUET Study

The DUET study (NCT01613118) is a phase 2, randomized, multicenter, double-blind, active-control trial in patients with biopsy-proven FSGS. Patients were randomized to 1 of 3 doses (200, 400, or 800 mg/day) of sparsentan or irbesartan (300 mg/day) and maintained through an 8-week double-blind phase. The primary endpoint was defined as reduction in UPCR after 8 weeks of treatment. The proportion of patients who achieved partial FSGS remission was evaluated as a secondary endpoint. Following the double-blind phase, patients had the option to continue into a 144-week OLE of treatment with sparsentan.[4]

The DUPLEX Study

The DUPLEX study (NCT03493685) is a global, randomized, multicenter, double-blind, active-controlled, phase 3 trial examining the safety and efficacy of sparsentan as compared to irbesartan in patients aged 8 to 75 years with biopsy-proven FSGS. Patients with UPCR ≥1.5 g/g at screening, eGFR ≥30 mL/min/1.73 m^2, and mean seated BP ≥100/60 mm Hg (patients ≥18 years) or above the 5th percentile for sex and height (<18 years) were eligible. After a 2-week washout period, 371 patients were randomized to receive either sparsentan or irbesartan, and subsequently dose titrated over 2 weeks to the maximum dose of either 800 mg/day sparsentan or 300 mg/day irbesartan, as tolerated.[5,10] Patients remained on maintenance doses of sparsentan or irbesartan during a 108-week double blind phase. Standard-of-care treatment, including RAASi, was resumed in Weeks 108-112. The primary efficacy endpoint was eGFR slope over 108 weeks of treatment, defined as eGFR total slope from Day 1 to Week 108 of treatment and eGFR chronic slope from Week 6 to Week 108 (following the initial acute effect of randomized treatment). The key secondary endpoint was percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112.[10] An additional interim endpoint was the proportion of patients achieving partial remission of proteinuria, defined as UPCR ≤1.5 g/g and a >40% reduction (FPRE)

at Week 36. Proportion of patients achieving complete remission of proteinuria (UPCR <0.3 g/g) at any time in the double-blind period was also examined. Safety was assessed by double-blind monitoring of adverse events and safety endpoints.[5,10]

Study Data

The PROTECT Study

In the PROTECT study, protocol allowances were made for the management of patients with worsening edema. Patients received half the target dose for the first 2 weeks after randomization. Dose tolerance was evaluated in a blinded manner at the Week 2 visit and was defined as systolic blood pressure >100 mm Hg and diastolic blood pressure >60 mm Hg after 2 weeks, and no AEs (eg, worsening edema) or laboratory findings interfering with the patient's continuation on study medication. Patients who did not tolerate the initial dose for any reason could discontinue the study medication and could re-start or reduce the study medication at the investigator's discretion.[6] Potassium-sparing diuretics were not to be coadministered with sparsentan in the PROTECT study.[6,7]

Safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals. TEAEs were reported in 187 (93%) patients taking sparsentan and 177 (88%) irbesartan-treated patients. SAEs were reported by 75 (37%) patients taking sparsentan and 71 (35%) patients taking irbesartan.[9]

Peripheral edema was similar in both groups, with no increases in body weight. Change from no edema at baseline to severe edema occurred in 0 sparsentan-treated patients and 2 irbesartan-treated patients. Change from no edema to moderate edema occurred in 2 patients taking sparsentan and none taking irbesartan. Diuretic use initiated on or after beginning study drug was reported in 49 (24%) sparsentan patients and 54 (27%) irbesartan patients. The most frequently used class of diuretics was thiazides, utilized by 35 (17%) and 42 (21%) sparsentan and irbesartan patients, respectively.[9]

The DUET Study

During the 8-week double-blind period, 6.8% (5/73) of patients in the sparsentan group were on a thiazide diuretic and 35.6% (26/73) were on a loop diuretic, and in the irbesartan group, 16.7% (6/36) of patients were on a thiazide diuretic and 22.2% (8/36) were on a loop diuretic (**Table 1**). A higher incidence of peripheral edema was reported in patients taking sparsentan compared to those on irbesartan. Across all 3 sparsentan dose cohorts, 12.3% (n=9) of patients experienced edema vs 2.8% (n=1) of patients taking irbesartan.[4]

Table 1. Diuretic Use During the Double-Blind Period of the DUET Study

Diuretic	Patients (N=109)	
	Irbesartan (n=36)	Sparsentan, All Doses (n=73)
Thiazide, n (%)	6 (16.7)	5 (6.8)
Hydrochlorothiazide	4 (11.1)	3 (4.1)
Chlorthalidone	0 (0)	1 (1.4)
Metolazone	2 (5.6)	1 (1.4)
Loop, n (%)	8 (22.2)	26 (35.6)
Furosemide	8 (22.2)	25 (34.2)
Bumetanide	0 (0)	1 (1.4)

After 8 weeks of treatment, there were no meaningful between-group differences in overall use and changes in diuretic treatment, or in severity of edema. In the sparsentan group, 11% (8/73) had new or increased diuretic use, compared with 11% (4/36) in the irbesartan group (**Table 2**). The proportion of patients in the sparsentan group with mild to moderate edema remained stable, whereas the proportion with severe edema rose from 2% to 5%. This occurred in parallel with an increase in the use of loop diuretics. At baseline, patients displayed varying degrees of edema, and there were no significant changes in body weight or N-terminal pro–B-type natriuretic peptide levels from baseline in sparsentan-treated patients. There were no study withdrawals or severe TEAEs related to edema.[4]

Table 2. Change in Diuretic Treatment During the Double-Blind Period of the DUET Study

Diuretic	Patients (N=109)	
	Irbesartan (n=36)	Sparsentan, All Doses (n=73)
All diuretics, n (%)		
New or increased	4 (11.1)	8 (11.0)
Reduced	1 (2.8)	1 (1.4)
Thiazide[a], n (%)		
New or increased	3 (8.3)	1 (1.4)
Reduced	0 (0.0)	1 (1.4)
Furosemide[b], n (%)		
New or increased	1 (2.8)	7 (9.6)
Reduced	1 (2.8)	0 (0.0)

[a]Thiazides included hydrochlorothiazide, chlorthalidone, and metolazone.
[b]No other loop diuretics change during the double-blind period.

The DUPLEX Study

At baseline, 9 (4.9%) of patients randomized to sparsentan and 6 (3.2%) patients randomized to irbesartan presented with moderate or severe edema. In the total study sample, 68 (37%) patients in the sparsentan group and 73 (39%) patients in the irbesartan group were taking diuretic medication. Throughout the study, AEs associated with fluid retention occurred in 47 (25.5%) of sparsentan-treated patients; the event was considered serious in 5 (2.7%) patients. Among

irbesartan-treated patients, fluid retention AEs were reported in 56 (29.9%) patients with serious events occurring in 12 (6.4%) patients. Diuretics were utilized by 106 (57.6%) and 102 (54.5%) patients in the sparsentan and irbesartan groups, respectively.[10]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AT_1, angiotensin II type 1; BP, blood pressure; COX-2, cyclooxygenase-2; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; KF, kidney failure; KRT, kidney replacement therapy; NSAID, nonsteroidal anti-inflammatory agent; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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