FILSPARI® (sparsentan)

Management of Edema in Patients With IgA Nephropathy in the PROTECT Study

Summary

Prescribing Information

The safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- In FILSPARI clinical studies, the most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia[1]
- In the PROTECT trial, peripheral edema occurred in 29 patients (14%) taking FILSPARI compared to 19 patients (9%) taking irbesartan[1]
- Fluid retention may occur with ERAs and has been observed in clinical studies with FILSPARI[1]
- 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]
- Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]

Study Data

- In the PROTECT study, potassium-sparing diuretics were not to be coadministered with sparsentan.[5,6] Protocol allowances were made for the management of patients with worsening edema, including use of other diuretics[5,7]
- Patients with edema were allowed to discontinue, pause and restart, or decrease the dose of study treatment while remaining in the study[5]
- Over 108 weeks of study treatment, peripheral edema occurred in 31 (15%) patients in the sparsentan group and 24 (12%) in the irbesartan group. Diuretic use initiated on or after beginning study drug was reported in 49 (24%) sparsentan patients and 54 (27%) irbesartan patients[8]
- No patients discontinued treatment due to edema[8]

Prescribing Information

The safety data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

The safety of FILSPARI was evaluated in PROTECT (NCT03762850), a randomized, double-blind, active-controlled clinical study in adults with IgAN.[1]

The data below reflect FILSPARI exposure in 202 patients with a median duration of 73 weeks (up to 110 weeks).[1]

The most common adverse reactions are presented in **Table 1**.[1]

Table 1. Adverse Reactions[a] Reported in ≥2% in Subjects Treated With FILSPARI

	FILSPARI (N=202) n (%)	Irbesartan (N=202) n (%)
Peripheral edema	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury	9 (4)	2 (1)
Transaminase elevations[b]	5 (2.5)	4 (2)

[a]Data presented include all Treatment-Emergent Adverse Events reported. [b]Elevations in ALT or AST >3-fold ULN reported as Adverse Events of Interest.

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]

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration. Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. No FILSPARI dose adjustment is needed. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC, which may increase the risk of FILSPARI adverse reactions.[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.[9-11]

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.[12] 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.[5] 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.[5,13] 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

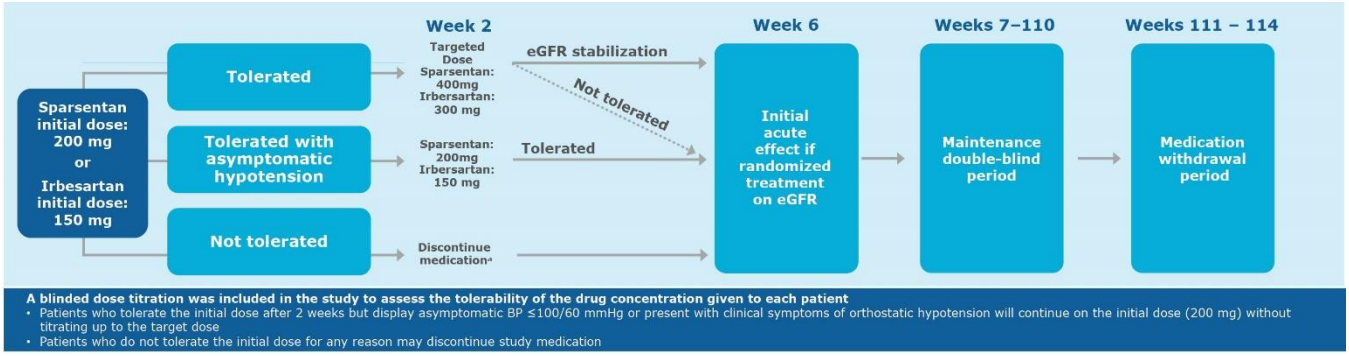
<1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[7] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[7,14]

Study Data

The PROTECT Study

In the PROTECT study, protocol allowances were made for the management of patients with worsening edema. Use of diuretics was prohibited during the trial. Target doses were 400 mg/day sparsentan and 300 mg/day irbesartan; patients received half of target dose for the first 2 weeks after randomization, with a goal to titrate to the target doses at Week 2 (**Figure 1**). 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.[5]

Figure 1. Blinded Dose Titration



[a]Patients who do not tolerate the initial dose will be encouraged to restart study medication throughout the study. Patients who do not tolerate study medication should continue in the study even if they permanently discontinue study medication.

Safety

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.[8]

Peripheral edema occurred in 31 (15%) patients in the sparsentan group and 24 (12%) in the irbesartan group. 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. No patients discontinued treatment due to edema. Hepatic TEAEs of interest of ALT or AST increasing >3× the ULN occurred in 5 (2%) patients in the sparsentan group and 7 (3%) patients in the irbesartan group. No cases of drug-induced liver injury occurred in either group.[8]

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; AUC, area under the curve; BP, blood pressure; C_{max}, maximum serum concentration; COX-2, cyclooxygenase-2; CYP3A, cytochrome P450 3A; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; IgA, immunoglobulin A; IgAN, IgA nephropathy; KF, kidney failure; KRT, kidney replacement therapy; NSAID, nonsteroidal anti-inflammatory drug; SAE, serious adverse event; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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