FILSPARI® (sparsentan) Use in Patients With Severely Decreased eGFR in IgA Nephropathy

Summary

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]
- This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPRI 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[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]
- KDIGO 2024 guidelines define eGFR 15-29 mL/min/1.73 m^2 as severely decreased (G4) and eGFR <15 mL/min/1.73 m^2 as kidney failure (G5)[5]
- The PROTECT study is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-control study of the efficacy and safety of sparsentan compared to irbesartan for the treatment of IgA nephropathy[6]

Study Data

The PROTECT Study

- The PROTECT study protocol excluded patients with an eGFR <30 mL/min/1.73 m^2 at screening[7]
- Data in patients whose eGFR declined to <30 mL/min/1.73 m^2 between screening and Day 1 are too limited to draw any conclusions

Prescribing Information

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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.[8-10]

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 in patients with IgA nephropathy compared to 300 mg of irbesartan.[11] 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.[12] 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.[6,12] 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.[13] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[13,14]

Study Data

The PROTECT Study

The PROTECT study protocol excluded any patients with an eGFR <30 mL/min/1.73 m^2 at screening; therefore, the efficacy and safety results were analyzed only for patients with an eGFR ≥30 mL/min/1.73 m^2 at screening.[7]

Between screening and Day 1, eGFR declined to <30 mL/min/1.73 m^2 in 15 (7%) patients in the sparsentan group and 5 (2%) patients in the irbesartan group[7]; however, the data are too limited to draw any conclusions.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; KF, kidney failure; KRT, kidney replacement therapy; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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