FILSPARI® (sparsentan)
Acute Kidney Injury

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 the PROTECT trial, acute kidney injury occurred in 9 (4%) patients treated with FILSPARI compared to 2 (1%) patients treated with irbesartan[1]
- Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury[1]
- Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (eg, patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI[1]
- Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI[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[5]:
  - TEAEs of AKI occurred in 12 (6%) patients taking sparsentan and 5 (2%) patients taking irbesartan
  - Serious TEAEs of AKI occurred in 4 (2%) patients taking sparsentan and 1 (<1%) patient taking irbesartan
  - Treatment discontinuations due to AKI occurred in 3 (1%) taking sparsentan and none taking irbesartan
- Reports of AKI were based on changes in serum creatinine between study visits rather than an acute hospital setting, and may reflect a gradual decline in kidney function rather than AKI[6]

Prescribing Information

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- In the PROTECT trial, acute kidney injury occurred in 9 (4%) FILSPARI-treated patients compared to 2 (1%) irbesartan-treated patients[1]
- Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury[1]
- Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (eg, patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI[1]
- Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI[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.[7-9]

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.[10] 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.[11] 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.[11,12] 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.[6] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[6,13]

Study Data

The PROTECT Study

While Kidney Disease Improving Global Outcomes (KDIGO) guidelines provide criteria for diagnosing AKI, reports of AKI adverse events in sparsentan studies may have been based on elevations in serum creatinine between study visits. KDIGO guidelines for diagnosing AKI are as follows[14]:

- Increased serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
- Increased serum creatinine ≥1.5× baseline (which is known or presumed to have occurred within the prior 7 days); or
- Urine volume <0.5 mL/kg/hour for 6 hours or more

While these KDIGO guidelines were described in the study protocol, they were designed for hospital settings where baseline values within given timeframes (ie, the preceding 48 hours to 7 days) are available. However, in interventional studies such as PROTECT, conducted in the outpatient setting with visits typically 12 weeks apart, repeat values across a shorter timeframe were not available in most cases. In such instances, at the investigator's discretion and based on the guidance provided in the protocol, reports of AKI were typically based on serum creatinine changes between study visits, which were several weeks apart. Changes in serum creatinine may therefore have been more reflective of gradual decreases in kidney function instead of clinical AKI.[6]

Interim Safety Data

AKI-associated TEAEs were reported in 9 subjects (4%) in the sparsentan group and 2 subjects (1%) in the irbesartan group.[6] None occurred during the first 6 weeks of treatment and none required dialysis.[15]

Three subjects in the sparsentan group experienced an AKI-associated TEAE that led to treatment discontinuation.[6]

Serious AKI-associated TEAEs were reported in 5 subjects (2%) in the sparsentan treatment group, 3 (1%) of which were considered possibly related to the study drug.[6] In the irbesartan group, 4 subjects (2%) reported serious AKI-associated TEAEs.[11] Cases rated as severe or serious were considered related to intercurrent illness, disease progression, or preceding and/or concurrent conditions rather than related to treatment.[6,15]

2-Year Safety Data

Over 2 years of treatment, TEAEs occurred in 187 (93%) patients taking sparsentan and 177 (88%) patients in the irbesartan group. AKI occurred in 12 (6%) and 5 (2%) patients in the sparsentan and irbesartan groups, respectively. Among sparsentan patients experiencing AKI, 4 (2%) were considered serious vs 1 (<1%) patient taking irbesartan. Three patients in the sparsentan group discontinued treatment due to AKI; there were no AKI-related discontinuations in the irbesartan group.[5]

In a subsample of patients in the PROTECT OLE study taking concomitant SGLT2 inhibitors, 2 of 39 patients (5%) experienced AKI.[16]

AKI in Additional Clinical Trials

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. Over 108 weeks of treatment, 172 (93.5%) patients in the sparsentan group and 174 (93%) patients in the irbesartan group reported at least 1 AE. AKI was reported in 8 (4.3%) patients taking sparsentan and 13 (7.0%) taking irbesartan. AKI was considered serious in 3 (1.6%) and 8 (4.3%) patients in the sparsentan and irbesartan groups, respectively.[17]

The EPPIK Study

The EPPIK study (NCT05003986) is a phase 2, global, open-label, single-arm, multicenter cohort study to evaluate the safety, efficacy, and PK of a liquid formulation of sparsentan in pediatric patients with selected proteinuric glomerular diseases. The primary objective of the EPPIK study is to examine long-term antiproteinuric and nephroprotective potential and safety in this pediatric population.[18] Over 12 weeks of sparsentan treatment, 1 patient experienced a serious TEAE of AKI.[19]

Abbreviations

AE, adverse event; AKI, acute kidney injury; 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; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; KF, kidney failure; KRT, kidney replacement therapy; OLE, open-label extension; PK, pharmacokinetics; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatine ratio; UPCR, urine protein-to-creatinine ratio.

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