FILSPARI® (sparsentan)
Hyperkalemia

Summary

Prescribing Information

- In the PROTECT trial, hyperkalemia occurred in 27 (13%) patients treated with FILSPARI compared to 21 (10%) patients treated with irbesartan[1]
- 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]

Background

- Hyperkalemia is known to occur in patients treated with AT_1 receptor antagonists, particularly in patients with advanced renal impairment or heart failure, or in patients taking potassium-increasing drugs[2]
- Hyperkalemia in response to sparsentan is a result of inhibition of aldosterone secretion and renal hemodynamic action that may lead to a reduction of GFR[3]

Study Data

- In the PROTECT study, after 36 weeks of treatment, rates of hyperkalemia were not different between the sparsentan and irbesartan groups and there were no hyperkalemia-related discontinuations[4]
    - In a 2-year confirmatory analysis of PROTECT study data, 32 (16%) patients taking sparsentan and 26 (13%) patients taking irbesartan experienced hyperkalemia[5]
- The DUET OLE study followed patients from 1 to <5 years. A total of 10.4 hyperkalemia cases per 100 patient years were reported[6]
- In the DUPLEX study over 108 weeks of treatment, hyperkalemia-associated AEs occurred in 37 (20.1%) patients taking sparsentan and 21 (11.2%) patients taking irbesartan[7]
- Among pediatric patients in the EPPIK study, 1 case of hyperkalemia was reported over 12 weeks of sparsentan treatment[8]

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.[9-11] 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.[12-14]

Hyperkalemia is known to occur in patients treated with AT_1 receptor antagonists, particularly in patients with advanced renal impairment or heart failure, or in patients taking potassium-increasing drugs.[2] Hyperkalemia in response to sparsentan is a result of inhibition of aldosterone secretion and renal hemodynamic action that may lead to a reduction of GFR.[3]

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.[15] 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.[16] 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.[16,17] 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.[18] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[18,19]

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.[11]

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.[7,20] 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.[7] 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.[7,20]

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.[21] Approximately 57 pediatric patients aged ≥1 to <18 years will be enrolled. EPPIK Population 1 will include ~30 patients aged 1 to <18 years with FSGS or treatment-resistant MCD. Population 2 will include ~27 patients aged 2 to <18 years with IgAN, IgAV, or Alport syndrome. Primary endpoints are the change from baseline in UPCR over a 108-week treatment period, incidence of TEAEs, SAEs, AEs leading to treatment discontinuation, and AEs of interest. Secondary endpoints include observed plasma PK concentration, steady-state PK parameters, change from baseline in UACR and eGFR over 108 weeks of treatment, and proportion of patients with FSGS or MCD histological patterns achieving partial remission (FPRE) in UPCR. Partial remission is defined as UPCR ≤1.5 g/g and >40% reduction in UPCR. Safety parameters are monitored throughout the duration of the study.[8,21]

Study Data

The PROTECT Study

After 36 weeks of treatment, laboratory tests indicated a small early increase in potassium levels in both PROTECT treatment groups, which then stabilized with a mean of <0.1 mmol/L through Week 82 and a maximum of 0.26 mmol/L at Week 106.[2] In PROTECT, changes in potassium were similar between the sparsentan and irbesartan treatment groups.[4]

In a 2-year confirmatory analysis of PROTECT study data, 32 (16%) patients taking sparsentan and 26 (13%) patients taking irbesartan experienced hyperkalemia.[5]

Overall, the AEs reported as hyperkalemia are based on increases in serum potassium from laboratory data rather than clinical consequences.[2]

The DUET Study

The DUET OLE followed patients from 1 to <5 years. A total of 10.4 hyperkalemia cases per 100 patient years were reported. In treatment Year 1, 7 (6.5%), cases occurred; 9 (10.3%), 3 (4.2%), 6 (10%), and 6 (11.1%) cases were reported in Years 2 to <5, respectively.[6]

The DUET OLE included 26 patients aged ≤21 years. In this pediatric subsample, a total of 10.4 cases of hyperkalemia per 100 patient years were reported. No cases of hpyerkalemia were reported in treatment Year 1, 3 (15%) cases occurred in Year 2, 2 (13%) cases occurred in Year 3, and 0 cases in Year 4.[22]

The DUPLEX Study

Over 108 weeks of treatment in the DUPLEX study, hyperkalemia-associated AEs occurred in 37 (20.1%) patients taking sparsentan and 21 (11.2%) patients taking irbesartan. There were no discontinuations due to hyperkalemic events.[7]

The EPPIK Study

Among pediatric patients in the EPPIK study, 1 case of hyperkalemia was reported over 12 weeks of sparsentan treatment.[8]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; KF, kidney failure; KRT, kidney replacement therapy; MCD, minimal change disease; OLE, open-label extension; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-

to-creatinine ratio.

References

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