# FILSPARI® (sparsentan)

# Dosing and Administration in Clinical Trials of IgA Nephropathy

## Summary


### Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[1]
- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs)[1]
- Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to 400 mg once daily, as tolerated. When resuming FILSPARI after an interruption, consider re-titration[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

*The PROTECT Study*

- Initial doses were sparsentan 200 mg/day or irbesartan 150 mg/day, and target doses were 400 mg/day sparsentan and 300 mg/day irbesartan[5]
- Dose tolerance was evaluated in a blinded manner at the Week 2 visit; patients who tolerated initial doses were increased to target doses. 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]

*The EPPIK Study*

- Sparsentan 80 mg/mL oral suspension is administered in a novel liquid formulation based on patient age and weight. For patients with FSGS or MCD, dose exposure is similar to an adult equivalent dose of 800 mg/day. For patients with IgAN, IgAV, or Alport syndrome, dose exposure is similar to an adult equivalent of 400 mg/day[6]

# Prescribing Information

## General Considerations

Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs)[1]

## Monitoring

Initiate treatment with FILSPARI only after measuring aminotransferase levels and total bilirubin. Avoid initiation in patients with elevated aminotransferases greater than 3 times ULN. Continue required monitoring monthly for the first 12 months after initiation or restarting following an interruption due to elevated transaminases, then every 3 months during treatment with FILSPARI.[1]

## Recommended Dosage

Initiate treatment with FILSPARI at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated. When resuming treatment with FILSPARI after an interruption, consider titration of FILSPARI, starting at 200 mg once daily. After 14 days, increase to the recommended dose of 400 mg once daily.[1]

## Administration

Instruct patient to swallow tablets whole with water prior to the morning or evening meal. Maintain the same dosing pattern in relationship to meals. If a dose is missed, take the next dose at the regularly scheduled time. Do not take double or extra doses.[1]

## Dosage Adjustment for Aminotransferase Elevations

If aminotransferase levels increase, adjust monitoring and treatment plan according to **Table 1**.[1]

Do not resume treatment in patients who have experienced clinical symptoms of hepatotoxicity or in patients whose hepatic enzyme levels and bilirubin have not returned to pretreatment levels.[1]

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

**Table 1. Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations Greater Than 3 Times ULN**

| ALT/AST levels | Treatment and monitoring recommendations |
|---|---|
| Greater than 3 times and less than or equal to 8 times ULN | Confirm elevation with a repeat measure.<br>If confirmed, interrupt treatment, and monitor aminotransferase levels and bilirubin at least weekly, and INR as needed, until the levels return to pretreatment values and the patient is asymptomatic.<br>Do not resume treatment if any of the following occurs without other cause found:<br>• ALT or AST greater than 3 times ULN and total bilirubin greater than 2 times ULN or INR greater than 1.5<br>• ALT or AST greater than 3 times ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (greater than 5% eosinophils)<br>• ALT or AST greater than 5 times ULN for more than 2 weeks<br>If treatment is resumed, initiate FILSPARI at 200 mg once daily, with reassessment of hepatic enzyme levels and bilirubin within 3 days. Close monitoring is required in these patients. |
| Greater than 8 times ULN | Stop treatment permanently if no other cause found. |

# 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 in patients with IgA nephropathy 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.[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.[5,11] 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 $m^2$.[12] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[12,13]

### 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.[14] 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.[6,14]

## Study Data

### Dosing and Administration in IgA Nephropathy

#### *The PROTECT Study*

On Day 1 following randomization, current ACEi and/or ARB therapies were discontinued for the duration of the study. Patients began initial doses of either study drug (sparsentan once-daily 200 mg) or active control (irbesartan once-daily 150 mg). Target doses were 400 mg/day sparsentan and 300 mg/day irbesartan; patients received half of the target dose for the first 2 weeks after randomization, with a goal to increase 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 (eg, serum potassium >5.5 mEq/L) interfering with the patient's continuation on study medication. Patients who tolerated initial doses were increased to target doses. 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. Decreases from and increases to target dose were permitted at any time throughout the study.[5]

### Figure 1. Dosing in the PROTECT Study


[a]On Day 1, patients will be randomized 1:1 to SPAR or IRB. [b]Patients will resume SOC treatment, including RAASi treatment. Where possible, the same treatment regimen the patient was on at study entry (ie, the same ACEi and/or ARB at the same dose[s]) should be used. [c]Starting dose of SPAR for the open-label extension will be 200 mg. Titration to 400 mg will be based on tolerability after 2 weeks of treatment in the open-label extension.

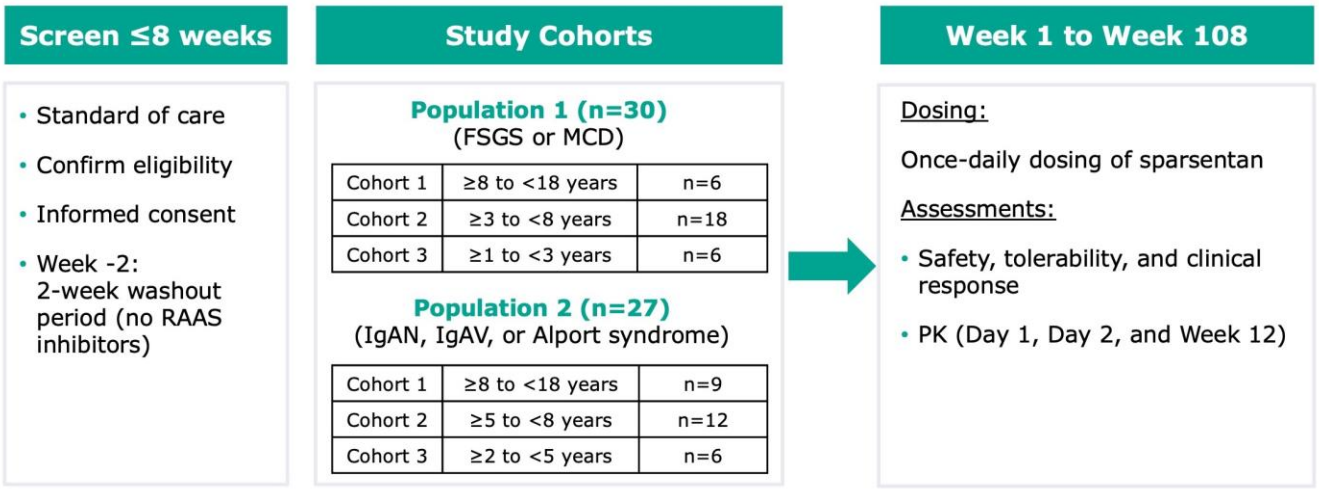
Safety data from the 2-year confirmatory analysis showed sparsentan to be well-tolerated, with a consistent safety profile comparable to irbesartan and no new safety signals.[15,16]

## Dosing and Administration in the EPPIK Study

### *Study Design*

Prior to enrollment, patients taking RAASi will undergo a 2-week washout period. Other antihypertensive medications, except endothelin inhibitors, are allowed for treatment of patients with hypertension. Following enrollment into Population 1 or 2, patients are further stratified into cohorts according to age. Patients are evaluated over 108 weeks and treated with once-daily dosing of liquid sparsentan. Patients are then returned to SOC for 4 weeks of follow-up. Safety, tolerability, and clinical response are assessed throughout the study (**Figure 2**).[6,14]

### Figure 2. EPPIK Study Design



Patients are randomly assigned to a PK assessment schedule. For all patients, PK plasma levels are assessed pre-dose on Day 1 and Week 12; an additional pre-dose PK plasma level measurement occurs on Day 2, ~24 hours after the first sparsentan dose on Day 1. At clinic visits following Week 12, plasma PK is assessed at either 1 hour and 2 hours post-dose, 2 hours and 4 hours post-dose, or 4 hours and 6 hours post-dose, depending upon the patient's assigned PK sampling schedule.[14]

### *Study Treatment*

Sparsentan 80 mg/mL oral suspension is administered in a novel liquid formulation; starting and target doses are determined based on patient age and weight (**Table 2**). For patients in Population 1 (FSGS or MCD), dose exposure is similar to an adult equivalent dose of 800 mg/day. For patients in Population 2 (IgAN, IgAV, or Alport syndrome), dose exposure is similar to an adult equivalent of 400 mg/day. Dosing titration is determined by patient age. Patients aged ≥2 years begin with 50% of the target dose and continue to Week 2; if tolerated, dose is increased to target. Patients aged <2 years begin with 25% of target dose up to Week 2; if tolerated, dose is increased to 50% target to Week 4. If tolerated at 50%, dose is increased to target. If necessary, doses may be modified, temporarily halted, or discontinued.[14]

**Table 2. Dosing in the EPPIK Study**

| Weight (kg) | Sparsentan 80 mg/mL | | | | | |
|---|---|---|---|---|---|---|
| | Population 1 (FSGS or MCD) Permitted Doses as % Target Dose | | | Population 2 (IgAN, IgAV, or Alport Syndrome) Permitted Doses as % Target Dose | | |
| | 25% | 50% | 100% | 25% | 50% | 100% |
| **≥2 years** | | | | | | |
| ≥40 | 2.5 mL | **5 mL** | 10 mL (800 mg) | 1.25 mL | **2.5 mL** | 5 mL (400 mg) |
| 30 to <40 | 1.875 mL | **3.75 mL** | 7.5 mL (600 mg) | 0.938 mL | **1.875 mL** | 3.75 mL (300 mg) |
| 20 to <30 | 1.25 mL | **2.5 mL** | 5 mL (400 mg) | 0.625 mL | **1.25 mL** | 2.5 mL (200 mg) |
| <20 | 0.625 mL | **1.25 mL** | 2.5 mL (200 mg) | 0.313 mL | **0.625 mL** | 1.25 mL (100 mg) |
| **<2 years** | | | | Not Applicable | | |
| 10 to <20 | **0.625 mL** | 1.25 mL | 2.5 mL (200 mg) | | | |
| 7 to <10 | **0.313 mL** | 0.625 mL | 1.25 mL (100 mg) | | | |

Bold indicates starting doses.

At data cutoff (April 5, 2023), 23 pediatric patients enrolled in the EPPIK study have received ≥1 dose of sparsentan oral suspension.[6,14] Sparsentan appeared to be safe and well-tolerated.[6]

## Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; $AT_1$, angiotensin II type 1; DBP,

diastolic blood pressure; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; $ET_A$, endothelin-1 type A; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A-associated vasculitis; INR, international normalized ratio; IRB, irbesartan; KF, kidney failure; KRT, kidney replacement therapy; MCD, minimal change disease; PK, pharmacokinetics; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor; SAE, serious adverse event; SBP, systolic blood pressure; SOC, standard of care; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

# References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