

New Drug Evaluation: sparsentan tablets, oral

Date of Review: December 2023

Generic Name: sparsentan

End Date of Literature Search: 09/12/2023

Brand Name (Manufacturer): Filspari™ (Travere Therapeutics, Inc)

Dossier Received: yes

Plain Language Summary:

- In 2023, the Food and Drug Administration (FDA) approved sparsentan, a medicine to treat a condition known as immunoglobulin A nephropathy (IgAN).
- Immunoglobulin A nephropathy is a type of kidney disease caused by buildup of a protein, called immunoglobulin, in the kidney. This causes damage to the kidneys and makes it harder for the kidneys to filter the blood.
- A small sample of tissue must be taken from the kidney to properly diagnose IgAN. Providers may also track levels of protein in the urine to help guide treatment.
- Treatment for IgAN includes:
 - Maintaining a healthy lifestyle including exercise, weight management, stopping smoking, and decreasing salt intake.
 - Keeping blood pressure under control. Some medicines that are normally used for blood pressure are given for kidney protection.
 - Prescribing medicines called glucocorticoids to reduce risk of kidney failure when the benefits of these medicines are greater than the risks of harmful side-effects.
- Sparsentan is a new medicine that lowers levels of protein in the urine for patients who have IgAN and are at risk of their disease worsening over a short time period. We do not know if sparsentan slows kidney decline in patients with IgAN.
- Studies with sparsentan showed that it may cause liver damage. Other side effects included arm and leg swelling, drops in blood pressure, dizziness, high potassium levels, and a low blood cell count that may have made patients feel weak and tired. Providers should not prescribe sparsentan for people who are pregnant or breastfeeding due to the possibility of harm to the developing baby.
- Use of sparsentan is only allowed under a special drug safety program (Risk Evaluation and Mitigation Strategies [REMS]) that is managed by the FDA. Prescribers, patients, and pharmacies must sign up for the program.
- We recommend that providers who prescribe sparsentan to a person enrolled in the Oregon Health Plan explain to the Oregon Health Authority why their patient needs sparsentan before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the evidence for efficacy of sparsentan in reducing proteinuria in adults with primary IgA nephropathy who are at risk of rapid disease progression?
2. What is the evidence for harms associated with the use of sparsentan?
3. Are there specific subpopulations that would be more likely to benefit or be harmed from the use of sparsentan?

Conclusions:

- Persistent proteinuria is a modifiable prognostic indicator for IgAN progression.¹ Sparsentan was approved by the Food and Drug Administration (FDA) under the Accelerated Approval pathway in February of 2023.^{1,2} Sparsentan is an endothelin type A receptor (ETAR) and angiotensin II type 1 receptor (AT1R) antagonist for use in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression due to proteinuria.^{1,2}
- The safety and efficacy of sparsentan was evaluated in one ongoing, randomized, double-blind, phase 3 trial in patients with biopsy-proven IgAN (PROTECT).¹⁻³ The study enrolled 406 patients with evidence of proteinuria >1 g/day, an eGFR of >30 ml/min/1.73m², and who were on a stable dose of a maximum tolerated angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB).¹⁻³ Patients on their current ACEi or ARB were switched to oral doses of either sparsentan 400 mg or irbesartan 300 mg once daily over a period of 110 weeks. A prespecified, unblinded interim analysis was planned at 36 weeks and was the basis of FDA approval.¹⁻³
- The FDA allowed the manufacturer to use the surrogate marker of urine protein-to-creatinine ratio (UPCR) for the primary efficacy endpoint.¹ It was determined that adults with primary IgAN may be at risk of rapid disease progression with a UPCR ≥ 1.5 g/g (normally 0.2 in unaffected individuals).¹ The change from baseline in proteinuria based on a 24-hour urine sample was evaluated for 281 patients at Week 36.¹⁻³ There was low-quality evidence that the adjusted mean percent change in urine protein to creatinine ratio (UPCR) compared to baseline was lower in the sparsentan group compared to the irbesartan group (-45% vs. -15%, respectively) with a mean ratio of 0.65 (95% CI, 0.55 to 0.77; p<0.0001).^{1,2} There is insufficient efficacy data of sparsentan beyond 36 weeks.^{1,2} It has not been established whether sparsentan slows kidney function decline in patients with IgAN.^{1,2}
- The most common adverse events that occurred during treatment in the sparsentan and irbesartan groups, respectively, were peripheral edema (14% vs. 9%), hypotension/orthostatic hypotension (14% vs. 6%), dizziness (13% vs. 5%), hyperkalemia (13% vs. 10%), and anemia (5% vs. 2%).¹⁻³
- Sparsentan prescribing information contains a boxed warning for risk of liver toxicity (up to 2.5% of patients) and embryo fetal toxicity (based on animal reproductive studies).^{1,2}
- Data are limited for use in people with risk factors for or have preexisting hepatic dysfunction.
- Sparsentan use is restricted to the FILSPARI Risk Evaluation and Mitigation Strategy (REMS) Program.^{1,2}

Recommendations:

- Implement prior authorization to ensure safe and appropriate use.
- Maintain sparsentan as non-preferred on the Oregon Health Plan (OHP) preferred drug list (PDL).

Background:

Immunoglobulin A nephropathy (IgAN) is a rare, progressive, inflammatory kidney disease that is the most common cause of end-stage renal failure in young adults.^{4,5} Among the various types of renal conditions, IgAN, or Berger's disease, is among the most frequently encountered primary glomerular diseases worldwide but its geographic distribution is varied.^{4,5} In the United States, it is estimated that the annual incidence of IgAN confirmed through biopsy is roughly 1 case per 100,000 persons.^{4,6-8} Compared to the US, the incidence of IgAN is higher among East Asian and Pacific Rim populations and lower in Africa.^{4,6-8} Certain risk factors such as a younger age of onset, male sex, hypertension, a decreased glomerular filtration rate (GFR), presence of proteinuria, and disease severity have all been identified as predictors of poor kidney prognosis in patients with IgAN.⁹ Immunoglobulin A nephropathy is more likely to manifest between the ages of 16-35 years but may be observed in patients younger or older with variable symptomatic presentation.¹⁰ Prevalence of IgAN is 2 to 6 times higher in males compared to females.⁸ Roughly 15-20% of patients with IgAN progress to end stage renal disease/dialysis within 10 years of diagnosis and 30-40% progress to failure within 20-30 years (**Table 1**).^{5,8,11-13}

Among the more prominent pathological features of IgAN is the deposition of IgA complexes in the mesangial region of the glomerulus.^{4,14} IgA molecules are one of 5 primary glycosylated immunoglobulins and are key factors in the regulation of mucosal homeostasis and immunity.⁴ IgA is secreted by plasma cells and provides a protective, anti-inflammatory function for the mucosa by inhibiting adhesion of pathogens and neutralizing toxins.¹⁵ The two forms of IgA, IgA1 and IgA2, differ in structure, role, and location found in the body.⁷ IgA1 makes up roughly 80% of the total IgA and is found mostly on the mucosal surfaces such as the lungs where it is more vulnerable to cleavage from bacterial proteases.⁷ IgA2 is found primarily in the colon.⁴ Deficiencies in IgA have been shown to result in a weakened mucosal barrier that is more susceptible to infection, especially in the gastrointestinal and upper respiratory tracts.⁸ Some studies suggest IgAN may be the result of a multi-step process influenced by genetic predisposition and environmental factors.^{4,15,16} When B-lymphocytes that produce galactose-deficient IgA1 enter systemic circulation and bone marrow, they raise the levels of serum Gal-deficient IgA1 (Gd-IgA1).^{15,17} These circulating abnormal IgA1 trigger the formation of anti-glycan IgA1 antibodies and immune complexes (IC).^{4,13} Due to the liver's inability to clear the aberrant IgA1, the ICs are deposited in the renal mesangium where they cause inflammation and lead to the glomerular damage.^{4,13,18,19}

IgAN may present as a broad range of clinical manifestations. The early stages of IgAN are often asymptomatic, with some patients displaying mild microscopic hematuria and/or slight proteinuria (<0.5 g/day) that can be detected via screening.^{10,18-20} Isolated microscopic hematuria with negligible proteinuria generally has a favorable prognosis.^{10,18,19} However, many children and adolescents and about 10% to 15% of young adult patients with IgAN present with macroscopic hematuria and concurrent infection of the upper respiratory tract or a gastrointestinal illness.^{10,18,19} As a progressive illness, IgAN rarely manifests with acute kidney failure.²⁰ Older adults with IgAN are more likely to present with a slow kidney decline with persistent proteinuria (e.g. >1 g/day), hematuria, hypertension, and a reduced estimated glomerular filtration rate (eGFR).²⁰ The classification of chronic kidney disease (CKD) stage according to GFR is listed in **Table 1**.²⁰ In adults 30 years of age or older, over half the patients with IgAN present with stage 3 to 5 progressive chronic kidney disease (CKD).^{10,18,19} Other complications may be evident such as rapidly progressive glomerulonephritis (RPGN) which results in a 50% or more decline in eGFR over 3 months or less.^{10,18,19} This rapid loss of kidney function is often associated with the presence of fibrous histological lesions known as cellular crescents.^{18,19} There are reports that almost half of patients with RPGN develop kidney failure within 1 year of diagnosis even when on immunosuppressive therapy.^{18,19}

Table 1: Stages of CKD²⁰

CKD Staging	Description	eGFR (ml/min/1.73 m ²)
1	Normal or High	≥90
2	Mildly Decreased	60-89
3a	Mild to Moderately Decreased	45-59
3b	Moderately to Severely Decreased	30-44
4	Severely Decreased	15-29
5	Kidney Failure	<15

Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate

There are no validated diagnostic serum or urine biomarkers for IgAN and a definitive diagnosis is only possible through kidney biopsy.²⁰ Due to variations in the sample collection and timing of the procedure, IgAN may display diverse pathological findings.¹⁴ Many studies have used kidney function and proteinuria as clinical outcome measures in patients with IgAN, but the findings are often difficult to distinguish from other acute inflammatory lesions that may produce sclerotic glomeruli or cellular crescents.^{14,21,22} The Modified Oxford classification and MEST-C score system (described in **Table 2**) has been widely used to determine the risk of a 50% decline in eGFR or ESRD (typically over 5 years) in patients with IgAN.²³⁻²⁵ Different pathologic variables comprise the MEST-C and

contribute to the overall prognosis.²³⁻²⁵ MEST-C scoring assigns a numerical value of 0 or 1 based on the presence of mesangial and endocapillary hypercellularity, and segmental glomerulosclerosis, or a score of 0, 1, or 2 for tubular atrophy/interstitial fibrosis.^{9,24,25}

Table 2. Oxford Classification/MEST-C Scoring System (modified)^{9,24,25}

Histology	Score
Mesangial hypercellularity	M0: Presence of mesangial hypercellularity in <50% glomeruli M1: Presence of mesangial hypercellularity in >50% glomeruli
Endocapillary hypercellularity	E0: No endocapillary hypercellularity E1: Presence of any endocapillary hypercellularity
Segmental glomerulosclerosis	S0: No segmental glomerulosclerosis S1: Presence of any segmental glomerulosclerosis
Tubular atrophy and interstitial fibrosis	T0: 0–25% tubular atrophy/interstitial fibrosis in cortical area T1: 26–50% tubular atrophy/interstitial fibrosis in cortical area T2: >50% tubular atrophy/interstitial fibrosis in cortical area
Cellular or fibrocellular crescents	C0: no cellular or fibrocellular crescents C1: Presence of cellular/fibrocellular crescents in 1%-25% glomeruli C2: Presence of cellular/fibrocellular crescents in >25% glomeruli
Key: M: mesangial hypercellularity; E: endocapillary hypercellularity; S: segmental glomerulosclerosis; T: tubular atrophy and interstitial fibrosis; C: crescent formation.	

Although the presence of cellular crescents are noted in the pathologic scoring, prominent IgAN guidelines recommend that number of crescents should not be used to determine the likelihood for progression of IgAN.^{9,20,24,25} The standardized MEST-C/Oxford Classification scores have been used to develop the International IgAN Prediction tool which, when combined with clinical data from kidney biopsy, assist clinicians in a more robust prognostic scoring system to help accurately predict risk of kidney decline in patients with IgAN.²⁵ The tool also considers other factors at the time of biopsy such as age, race, eGFR, blood pressure, presence of proteinuria, and supportive drug therapy (e.g. ACEi/ARB and immunosuppressive agent use) to predict risk of IgAN progression.²⁶ Other biomarkers have been proposed such as kidney inflammation, anemia, hyperuricemia, increased plasma osmolality, and elevated neutrophil:lymphocyte ratio but these markers have yet to be validated.²⁷ Even with advances in prediction models and diagnostic tools, there is still an unmet need for noninvasive biomarkers to support the evaluation of real-time disease activity in patients with IgAN.²⁷

Proteinuria is a risk factor for renal disease and persistent proteinuria in excess of 1 g/d over 6 to 12 months is associated with increased risk of progression in IgAN.⁹ In a study of 1155 patients, a statistically significant difference in 10-year kidney survival was demonstrated in patients with sustained proteinuria of 0.5-1 g/day compared to >1 g/d, which included a 10-year dialysis-free survival of 94% (95% CI: 90%–98%), and also a 20-year dialysis-free survival of 89% (95% CI: 82%–96%).²⁰ A 24-hour urine protein (24h-UP) is the standard test used to determine proteinuria.²⁶ Although the 24h-UP collection may be a challenge for some patients, it is particularly useful to discern small graduations of proteinuria given the association between increased disease risk and changes in proteinuria from 1-2 g/d and particularly >2 g/d.²⁶ Other less cumbersome methods to determine proteinuria include the urine protein to creatinine ratio (UPCR; normal ratio <0.2).²¹ Since protein excretion and urinary creatinine are assumed to be constant over time, the UPCR from a single urine sample has been used as a substitute

for a 24h-UP.^{21,26} The UPCR has been found to be reliable predictor of kidney function in a number of chronic renal disease studies.^{5,21,26} However, there is also evidence to suggest that UPCR has a relatively poor correlation with 24 h-UP when proteinuria is over 1 g/d.^{5,21,26}

Although treatment for IgAN is dependent upon stage and symptoms, comprehensive supportive care therapy is first-line to help preserve and slow decline of renal function.^{20,28} Supportive care may necessitate lifestyle modifications such as increased exercise and weight management strategies, smoking cessation, and restriction of sodium intake (<2 g/d).^{9,20,28} Maximum dose (or maximum tolerated dose) of renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are recommended to decrease the risk of kidney failure by reducing proteinuria independent of the presence of hypertension.^{20,28,29} For patients with IgAN and comorbid hypertension, the target blood pressure is 120/75 mm Hg and proteinuria <0.5 g/d (See **Table 3**).^{5,15} Although RAAS blockade may provide a benefit in patients with IgAN and hypertension, the long-term impact on other renal and/or cardiovascular endpoints including mortality is unclear.²⁰ For patients with high risk of progressive CKD and already on maximal supportive care, a 6-month trial of glucocorticoid therapy may be warranted.^{13,20} Immunosuppressive therapy with corticosteroids should be considered only when benefits of proteinuria reduction outweigh risks of toxicity.^{20,28} Budesonide delayed-release (DR) capsules (TARPEYO) is a corticosteroid indicated to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression as defined by a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.³⁰ Budesonide for IgAN treatment was approved based on a surrogate marker of proteinuria reduction although it has not been established whether oral budesonide slows kidney function decline in patients with IgAN.³⁰

Table 3. Comprehensive Supportive Therapy for Patients with IgAN^{5,15}

<ul style="list-style-type: none">• ACEi or ARB irrespective of whether patients have high blood pressure →Target: blood pressure 120/75 mm Hg and proteinuria <0.5 g/d
<ul style="list-style-type: none">• Statin therapy if persistent hyperlipidemia
<ul style="list-style-type: none">• Low-sodium diet (<2 g/d) →24-hour urinary sodium excretion can be used to verify dietary consumption
<ul style="list-style-type: none">• Advice on smoking cessation
<ul style="list-style-type: none">• Avoidance of NSAIDs and other nephrotoxic drugs
<ul style="list-style-type: none">• Healthy weight target

It has been reported that endothelin-1 and angiotensin II may contribute to the pathogenesis of IgAN via the endothelin type A receptor (ETAR) and angiotensin II type 1 receptor (AT1R) pathway, respectively, and that antagonism of these receptors may result in a reduction of proteinuria.³² Sparsentan is an ETAR and AT1R antagonist approved by the FDA to treat patients with IgAN.^{1,2} Both angiotensin II and certain isoforms of endothelin are strong vasoconstrictors and play a major role in the development of hypertension, CVD, and CKD.^{32,33} Endothelin (ET) is a polypeptide produced by endothelial cells and is also present in the epithelial and mesangial cells within the renal system.^{32,33} There are 3 known isoforms of ET and ET-1 has been shown to have the largest influence on renal vasoconstriction.^{32,33} Various stimuli that increase renal ET-1 (e.g. acidosis, hyperglycemia, angiotensin II, pro-inflammatory cytokines, etc.) lead to toxic effects on renal function and eventual decline.^{32,33} Inhibition of both RAAS and ET-1 may, therefore, be a potential target to slow the course of progressive kidney dysfunction in patient with IgAN.³²

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Sparsentan was approved by the FDA under the Accelerated Approval pathway in February of 2023.^{1,2} Sparsentan is indicated for adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.^{1,2} FDA labeling suggests that sparsentan should be used in people with IgAN confirmed through biopsy.^{1,2} Prior to treatment, any use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), and/or aliskiren should be discontinued.²

Sparsentan is being studied in one ongoing, randomized, double-blind, phase 3 trial in patients with biopsy-proven IgAN (PROTECT).^{1,3} The study enrolled 406 patients with evidence of proteinuria ≥ 1 g/day, an eGFR of ≥ 30 ml/min/1.73m², and who were on a stable dose of a maximum tolerated ACEi or ARB for at least 12 weeks or longer.^{1,3} Per study protocol, patients discontinued their ACEi or ARB one day prior to the start of the study.^{1,3} Although the trial design excluded participants with recent systemic corticosteroid and/or immunosuppressive therapy, if warranted, it was provided in addition to study medication at the discretion of the investigator.^{1,3} Patients were randomized 1:1 to receive oral doses of either sparsentan 400 mg or irbesartan 300 mg once daily over a period of 110 weeks.^{1,3} Doses for both sparsentan and irbesartan were titrated over a 2-week period until target doses were reached.^{1,3} The protocol had a prespecified, unblinded interim analysis planned at 36 weeks.^{1,3} The primary endpoint for the trial was the change in proteinuria from baseline based on a 24-hour urine sample at Week 36, while the confirmatory endpoint was the rate of change in eGFR over a 110-week period (approximately 2 years) after initiation of therapy.^{1,3} At baseline, both the sparsentan and irbesartan groups had similar characteristics including mean eGFRs (57.1 mL/min/1.73 m² and 55.6 mL/min/1.73 m², respectively), mean urinary protein excretion (2.1 g/day and 2.2 g/day, respectively), and mean UPCR values (1.4 g/g and 1.5 g/g, respectively).^{1,3}

Of the 406 participants enrolled, results of the first 281 patients were analyzed for the interim analysis.^{1,2} At week 36, low-quality evidence showed the adjusted mean percent change in UPCR compared to baseline was lower in the sparsentan group compared to the irbesartan group (-45% vs. -15%, respectively) with a mean ratio of 0.65 (95%CI, 0.55 to 0.77; p<0.0001).^{1,2} The clinical significance of this magnitude of change is unclear.

Trial findings were limited to the unblinded interim analysis at week 36 which included only a portion of all randomized participants (full study results not yet available). The mean age of subjects in the interim analysis set was 46 years of age. IgAN typically manifests in patients who are in their late teens to early 30s, therefore, the study may have included a high proportion of patients with more late-stage disease. It is unclear if younger patients on this therapy would respond in a similar manner. There was no evidence of participant assessment of a baseline MEST-C score or similar validated tool for between-group comparison. There were more individuals in the sparsentan group on maximum labeled dose of ACEis or ARBs as well as other hypertensive medications compared to the irbesartan group (65% vs 62%, and 44% vs 41%, respectively) but the effects of these slight differences on the outcome measures were unclear. The exclusion criteria around hepatotoxicity and CVD make safety and effectiveness uncertain in people with risk factors for these conditions. Also, the investigators were unable to perform a full assessment of important features such as microscopic or macroscopic hematuria given the use of a central laboratory for analysis. To date, there is limited data available whether the surrogate outcome of proteinuria reduction has a long-term clinical significance for patients with IgAN. To understand sparsentan's true place in therapy, additional research with a larger study population over a longer duration may be needed with an emphasis in primary survival endpoints and functional outcomes. The findings from the full confirmatory clinical trial will not be available until its completion (anticipated 10/2023; report to be submitted to FDA 02/2024).¹

Clinical Safety:

There were 404 patients included in the safety population.¹⁻³ The proportion of serious adverse events (SAEs) and discontinuations due to an adverse event were similar between groups. There were no reported deaths. The most common adverse events that occurred during treatment in the sparsentan and irbesartan groups, respectively, were peripheral edema (14% vs. 9%), hypotension/orthostatic hypotension (14% vs. 6%), dizziness (13% vs. 5%), hyperkalemia (13% vs. 10%), and anemia (5% vs. 2%).¹⁻³ There were more participants in the sparsentan group that required dose reductions after titration compared to those treated with irbesartan (13% vs 9%, respectively). There was a decrease in hemoglobin (> 2 g/dL from baseline and below the lower limit of normal) observed in 11% of sparsentan and 5% of irbesartan recipients.¹⁻³ However, in the study no patient discontinued treatment because of anemia or decreased hemoglobin.¹⁻³ The adverse reactions reported during the PROTECT trial are summarized in **Table 4**.

Table 4. Adverse Reactions Reported In 5% Or More Of Patients Treated with Sparsentan Compared to Irbesartan¹⁻³

Adverse Reactions	Sparsentan (n=202)	Irbesartan (n=202)
Peripheral edema	14%	9%
Hypotension (including orthostasis)	14%	6%
Dizziness	13%	5%
Hyperkalemia	13%	10%
Anemia	5%	2%

Sparsentan prescribing information contains a boxed warning of liver toxicity risk and embryo fetal toxicity.² Endothelin receptor antagonists are associated with risk of elevated aminotransferases and liver toxicity/failure.² Roughly 2% of patients of sparsentan-treated patients had increases in aminotransferases of more than three times the upper limit of normal, however, the increases were asymptomatic and reversible upon discontinuation of the drug.² Sparsentan is contraindicated during pregnancy due to animal studies that reported the possibility of fetal harm. Patients are also cautioned to avoid breastfeeding during sparsentan administration.² Sparsentan is available through a Risk Evaluation and Mitigation Systems (REMS) program due to observed hepatotoxicity.² The REMS program requires documentation of serum aminotransferases and total bilirubin before treatment, monthly for 12 months, and then every 3 months in addition to pregnancy testing monthly for those with childbearing potential during treatment.² If patient has elevated aminotransferase levels greater than 3 times the upper limit of normal, treatment is not recommended.² Sparsentan use is contraindicated with concomitant RAAS inhibitors, ERAs, or aliskiren.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Improved survival
- 2) Stabilization of kidney function
- 3) Time to renal failure
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Mean percent change from baseline in urine protein-to-creatinine ratio

Table 5. Pharmacology and Pharmacokinetic Properties.^{1,2}

Parameter	
Mechanism of Action	ETAR and AT1R antagonist. Endothelin-1 and angiotensin II are thought to contribute to the pathogenesis of IgAN via these receptors, and sparsentan has a high affinity for them, with a greater than 500-fold selectivity over the endothelin type B and angiotensin II subtype 2 receptors.
Oral Bioavailability	NA
Distribution and Protein Binding	Vd = 61.4L; Protein binding >99% (>90% binding to albumin)
Elimination	Feces (80%); Renal (2%)
Half-Life	9.6 hours
Metabolism	Cytochrome P450 3A

Abbreviations: AT1R = angiotensin II type 1 receptor; ETAR = Endothelin type A receptor; IgAN = immunoglobulin A nephropathy ; NA = not applicable; Vd = volume of distribution.

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Heerspink et al ^{1,3} DB, PG, AC, Phase 3, RCT	1. sparsentan 400 mg once daily 2. irbesartan 300 mg once daily 36 weeks	<u>Demographics:</u> Mean age: 46 years Male: 70% <u>Race:</u> -White 67% -Asian 29% -Black or African American 1% Hx of HTN: 70% Age at IgAN dx: 38.5 years Mean UPCr 1.4 g/g Urinary protein excretion: 1.8 g/day Mean eGFR: 57 ml/min/1.73m ² Serum albumin: 41 g/L ACEi/ARB max dose: 63% Baseline concomitant agents: -Antihypertensive 42% -Lipid lowering 55% <u>Key Inclusion Criteria:</u> -Biopsy-proven IgAN	<u>ITT:</u> 1.202 2.202 <u>mITT:</u> 1.141 2.140 <u>PP:</u> 1.133 2.128 <u>Attrition:</u> 1. 23 (11%) 2. 39 (19%)	<u>Primary Endpoint:</u> Mean* percent change in UPCr from baseline to week 36: 1. -45% (95% CI -51% to -38%) 2. -15% (95% CI -24% to -4%) Mean ratio: 0.65 (95% CI 0.55 to 0.77) p-value <0.0001 *=adjusted geometric	NA for all	<u>Any SAE</u> 1. 28 (13.9%) 2. 27 (13.4%) <u>Discontinued drug due to AE:</u> 1. 16 (7.9%) 2. 9 (4.5%) <u>Peripheral edema:</u> 1. 29 (14%) 2. 19 (9%) <u>Hypotension:</u> 1. 28 (14%) 2. 12 (6%) <u>Dizziness:</u> 1. 27 (13%) 2. 11 (5%) <u>Hyperkalemia:</u> 1. 27 (13%)	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (Low) Randomized using predefined computer-generated schedule. Randomization stratified via eGFR and UP excretion. Baseline characteristics similar between groups. <u>Performance Bias:</u> (Unclear) Study drug and active control identical in appearance and packaging. Participants, investigators and clinical staff blinded except for the data monitoring committee, SAE monitoring contact, and the “limited unmasked team” responsible for interim analysis (precluded from further participation). BP meds could be initiated/titrated at investigator’s discretion until target goal reached (125/75 mmHg). <u>Detection Bias:</u> (Unclear) Proteinuria and albuminuria were assessed by 24-h urine collection at each study visit and analyzed at a central laboratory but blinding process not described. <u>Attrition Bias:</u> (Unclear) Only portion of randomized subjects (281/406) had 9-month UP/C measurement at the time of interim analysis; missing data was imputed using a multiple imputation (MI) procedure which was not described in detail.

		<p>-24hr urine protein excretion ≥ 1.0 g/day after 12 weeks RAAS inhibition -eGFR ≥ 30 ml/min/1.73m² -BP $\leq 150/100$ mmHg</p> <p><u>Key Exclusion Criteria:</u> -IgAN secondary to another condition or IgA vasculitis -systemic immunotherapy (including corticosteroids) within previous 3 months - >25% glomeruli cellular crescents on renal biopsy within 6 mos of screening -CVD or major hepatic conditions -Concomitant use of any prohibited medications: RAAS inhibitors, endothelin inhibitors, Potassium-sparing diuretics, thiazolidinediones, SGLT-2 inhibitors, amphetamines, digoxin</p>			2. 21 (10%)	<p><u>Reporting Bias:</u> (Low) Study followed original trial design. <u>Other Bias:</u> (High) Study was funded by the manufacturer. Funding source had role in data collection, data interpretation and analysis.</p> <p>Applicability: <u>Patient:</u> Results are most applicable to male patients in their mid-teens to mid-30s of East Asian/Pacific Rim or Northern European heritage. Study enrolled primarily male population with limited diversity (White 67%, Asian 29%). Study excluded 265/671 (39%) patients initially screened including participants recently prescribed glucocorticoids and also those with >25% glomeruli cellular crescents, which may have decreased proportion of patients with rapidly progressing disease. <u>Intervention:</u> The dose of sparsentan is appropriate based on phase 2 studies. <u>Comparator:</u> Active treatment with RAS inhibitor such as irbesartan in patients with proteinuria >0.5 g/d is standard of care. <u>Outcomes:</u> Substantial reduction in proteinuria as a reasonably likely surrogate endpoint for IgAN disease progression.¹ <u>Setting:</u> 156 sites, 18 countries</p>
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Abbreviations: AC=active control; ACEi = angiotensin converting enzyme inhibitors; AE = adverse event; ARB = angiotensin (II) receptor blocker; ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; DB = double blind; D/C = discontinued; eGFR = estimated glomerular filtration rate; GMR = Ratio of Geometric Mean; HTN = hypertension; IAS = interim analysis set; IgA(N) = Immunoglobulin A (nephropathy); ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PG = parallel group; PP = per protocol; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium glucose co-transporter-2 inhibitors; UP = urinary protein; UPCR = urine protein-to-creatinine ratio

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FILSPARI™ safely and effectively. See full prescribing information for FILSPARI™.

FILSPARI™ (sparsentan) tablets, for oral use

Initial U.S. Approval: 2023

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- FILSPARI is only available through a restricted distribution program called the FILSPARI Risk Evaluation and Mitigation Strategies (REMS) because of these risks (5.3):
- Some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure (5.1).
- Measure liver aminotransferases and total bilirubin prior to initiation of treatment and ALT and AST monthly for 12 months, then every 3 months during treatment (2.2, 2.5, 5.1).
- Interrupt treatment and closely monitor patients developing aminotransferase elevations more than 3x Upper Limit of Normal (ULN) (2.2, 2.5).
- Based on animal data, FILSPARI can cause major birth defects if used during pregnancy (4, 5.2, 8.1).
- Pregnancy testing is required before, during, and after treatment (2.2, 4, 5.2, 8.1).
- Patients who can become pregnant must use effective contraception prior to initiation of treatment, during treatment, and for one month after (4, 5.3, 8.1, 8.3).

INDICATIONS AND USAGE

FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g (1, 12.1).

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI 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.

DOSAGE AND ADMINISTRATION

- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs) or aliskiren (2.1, 4, 7.1).
- 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 (2.3).
- Instruct patients to swallow tablets whole with water prior to the morning or evening meal (2.4).

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg and 400 mg (3).

CONTRAINDICATIONS

- Pregnancy (4).
- Do not coadminister FILSPARI with angiotensin receptor blockers, endothelin receptor antagonists, or aliskiren (4).

WARNINGS AND PRECAUTIONS

- Hepatotoxicity (5.1)
- Embryo-Fetal Toxicity (5.2)
- Hypotension (5.4)
- Acute Kidney Injury (5.5)
- Hyperkalemia (5.6)
- Fluid Retention (5.7)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Travele Therapeutics at 1-877-659-5518 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Renin-Angiotensin System (RAS) inhibitors and ERAs: Contraindicated. Increased risk of hypotension, hyperkalemia (2.1, 4, 7.1).
- Strong CYP3A inhibitors: Avoid concomitant use. Increased sparsentan exposure (2.6, 7.2, 12.3).
- Moderate CYP3A inhibitors: Monitor adverse reactions. Increased sparsentan exposure (7.2, 12.3).
- Strong CYP3A inducers: Avoid concomitant use. Decreased sparsentan exposure (7.3, 12.3).
- Antacids: Avoid use within 2 hours before or after use of sparsentan. May decrease exposure to sparsentan (7.4, 11).
- Acid reducing agents: Avoid concomitant use. May decrease exposure to sparsentan (7.4).
- Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase (COX-2) inhibitors: Monitor for signs of worsening renal function. Increased risk of kidney injury (7.5).
- CYP2B6, 2C9, and 2C19 substrates: Monitor for efficacy of the concurrently administered substrates. Decreased exposure of these substrates (7.6, 12.3).
- Sensitive P-gp and BCRP substrates: Avoid concomitant use. Increased exposure to substrates (7.7, 12.3).
- Agents Increasing Serum Potassium: Increased risk of hyperkalemia, monitor serum potassium frequently (5.6, 7.8).

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2023

Appendix 2: Proposed Prior Authorization Criteria

Sparsentan

Goal(s):

- To promote use that is consistent with medical evidence and product labeling in patients with immunoglobulin A nephropathy (IgAN).
- To ensure appropriate use of sparsentan in populations with clinically definite IgAN.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- Up to 12 months

Requires PA:

- Sparsentan

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient ≥ 18 years of age with diagnosis of IgAN confirmed by biopsy?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Does the patient have an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m ² ?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy for a patient who has received ≥ 6 months of initial therapy with this agent?	Yes: Go to Renewal Criteria	No: Go to #5
5. Is the medication going to be used in combination with any renin-angiotensin-aldosterone antagonists (e.g. angiotensin converting enzyme inhibitors or angiotensin receptor blockers), endothelin receptor antagonists [ERAs], or aliskiren?	Yes: Pass to RPh. Deny; medical appropriateness Use of sparsentan and any these agents is contraindicated.	No: Go to #6

Approval Criteria		
6. Is the prescriber a specialist in the management of IgAN (e.g. nephrologist)?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Is the patient at high risk of disease progression, defined as a 24-hour urine collection that indicates: <ul style="list-style-type: none"> Proteinuria > 1.0 g/day; -OR- <ul style="list-style-type: none"> Urine protein-to-creatinine ratio ≥ 1.5 g/g? 	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Will the prescriber attest that the patient received the maximum or maximally tolerated dose of <u>ONE</u> of the following for ≥ 12 weeks prior to starting sparsentan: <ul style="list-style-type: none"> Angiotensin converting enzyme inhibitor Angiotensin receptor blocker -OR- is there documentation that the patient has an intolerance or contraindication to renin-aldosterone-angiotensin system (RAAS) inhibitors?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness
9. Has the patient received ≥ 3 months of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification, according to the prescriber?	Yes: Approve for 9 months	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the prescriber documented a positive patient response to sparsentan therapy such as: <ul style="list-style-type: none"> eGFR that is not declining? Stabilization or improvement of proteinuria? No progression to dialysis? 	Yes: Approve for 1 year	No: Pass to RPh. Deny; medical appropriateness