Sparsentan (FILSPARI)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Sparsentan is an endothelin and angiotensin II receptor antagonist, with high affinity for both the endothelin type A receptor (ETAR) and the angiotensin II type 1 receptor (AT1R). As noted per the manufacturer prescribing information, endothelin-1 and angiotensin II are thought to contribute to the pathogenesis of immunoglobulin A nephropathy (IgAN) via the ETAR and AT1R, respectively.

Indication(s) Under Review in This Document

- Sparsentan is FDA approved to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.
- The indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether sparsentan 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 Form(s) Under Review

- Sparsentan is available as 200 mg and 400 mg tablets.
  - Sparsentan is administered once daily and should be swallowed whole with water prior to the morning or evening meal.
  - Initial dosing is 200 mg orally once daily. After 14 days, it is recommended to increase the dose to 400 mg once daily, as tolerated. Refer to the prescribing information for additional information on dosing and administration.

REMS

- Use of sparsentan is restricted to the FILSPARI Risk Evaluation and Mitigation Strategy (REMS) Program (refer to the product information and VA Specialty Distribution on PBM Sharepoint).

Clinical Evidence Summary[1-2]

Efficacy Considerations[1-2]

- PROTECT: Data for approval of sparsentan is based on a prespecified interim analysis at week 36 of an ongoing Phase 3 multicenter double-blind active-controlled trial in patients with IgAN with persistent proteinuria at high risk of disease progression despite treatment with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB). Patients were randomized to treatment with sparsentan or irbesartan with planned trial duration of 114 weeks; an open-label extension period of up to 156 weeks includes a substudy evaluating the addition of a sodium-glucose cotransporter-2 (SGLT2) inhibitor to sparsentan.
- Inclusion and exclusion criteria:

- Main inclusion criteria: patients with biopsy-proven primary IgAN; proteinuria ≥ 1 g/day at screening; estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m2 at screening; on a stable dose of an ACEI and/or ARB at the maximum tolerated dose and at least one-half of the maximum labeled dose for at least 12 weeks prior to screening; and systolic blood pressure (SBP) ≤ 150 mmHg and diastolic blood pressure (DBP) ≤ 100 mmHg.
- Exclusion criteria included: patients with IgAN secondary to another condition or IgA vasculitis; presence of cellular glomerular crescents in > 25% of glomeruli on renal biopsy (if biopsy available within 6 months of screening); or a cause of chronic kidney disease (CKD) in addition to IgAN; history of organ transplantation (other than corneal transplants); systemic immunosuppressive medications (including corticosteroids) for > 2 weeks within 3 months of screening; history of heart failure or previous hospitalization for heart failure or unexplained dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, and/or peripheral edema; clinically significant cerebrovascular disease or coronary artery disease within 6 months of screening; jaundice, hepatitis, or known hepatobiliary disease or elevations of transaminases (ALT/AST) > 2 times upper limit normal (ULN) at screening; history of malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma within the past 2 years; hematocrit < 27% or hemoglobin < 9 g/dL at screening; potassium > 5.5 mEq/L at screening; history of alcohol or illicit drug use disorder; serious side effect or allergic reaction to any ARB or endothelin receptor antagonist (ERA); pregnancy, or planning to become pregnant, or breastfeeding.

- The primary outcome measure was the change in proteinuria (UPCR) from baseline to week 36 in the two treatment groups and is included in Table 1 below.

Table 1: Primary Outcome (PROTECT)[2]

Patients with IgAN	Sparsentan (N=202)	Irbesartan (N=202)
Adjusted geometric mean (GM) % change from baseline at week 36 (95% CI)	-49.8% (-55.0%, -44.0%)	-15.1% (-23.7%, -5.4%)
Ratio of adjusted GM relative to baseline at week 36 (95% CI) (sparsentan vs. irbesartan)	0.59 (0.51, 0.69)[a]	

[a] P<0.0001

- The secondary outcome measures of rate of change in eGFR over a 52-week period (week 6 [after the initial acute effect] to week 58), over a 104-week period (week 6 to week 110), and over a 110-week period (day 1 to week 110) are pending clinical trial completion.
- Enrolled patients had any renin-angiotensin system inhibitors, or other prohibited medications discontinued. Patients were then randomized to sparsentan (400 mg once daily after 200 mg once daily for 14 days) or irbesartan (300 mg once daily following 150 mg once daily for 14 days). There was no washout period. Rescue immunosuppressive therapy was at the discretion of the provider. Use of an SGLT2 inhibitor was not allowed in the active-controlled clinical trial phase.
- Baseline characteristics included mean age 46 years, 70% male, 67% White, 29% Asian, 1% Black or African American, and 8% Hispanic or Latino ethnicity. It was noted that approximately 77% had a history of hypertension, 12% had diabetes or impaired fasting glucose, and 53% hematuria. Baseline UPCR (g/g) was 1.3 in patients randomized to sparsentan and 1.2 in the irbesartan treatment group. Mean (SD) baseline eGFR was 57(24) mL/min/1.73m2 at baseline. The median treatment duration at the interim efficacy end date was 64.1 weeks.

Safety Results from Clinical Trials[1]

- Per the prescribing information, the most common adverse reactions with sparsentan in patients with IgAN in the PROTECT clinical trial are reported in Table 2 below.

Table 2: Adverse Reactions Reported in >=2% Patients Treated with Sparsentan[1]

Adverse Reaction	Sparsentan N=202 (%)	Irbesartan N=202 (%)
Peripheral edema	14	9
Hypotension (including orthostatic hypotension)	14	6
Dizziness	13	5
Hyperkalemia	13	10
Anemia	5	2
Acute kidney injury	4	1
Transaminase elevations	2.5	2

Safety Considerations[1]

- **Boxed Warning: Hepatotoxicity and Embryo-Fetal Toxicity**
  - Because of the risks of hepatotoxicity and birth defects, sparsentan is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients, and pharmacies must enroll in the program.
  - Hepatotoxicity: some ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3 times the ULN have been observed in up to 2.5% of patients treated with sparsentan, including cases confirmed with rechallenge. Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3 times the ULN. Sparsentan should generally be avoided in patients with elevated aminotransferases (greater than 3 times the ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.
  - Embryo-Fetal Toxicity: sparsentan can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment, and one month after discontinuation of treatment with sparsentan. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with sparsentan.
- **Contraindications:**
  - Pregnancy
  - Concomitant ARBs, ERAs, or aliskiren
- **Warnings / Precautions**:
  - Hepatotoxicity: elevations in ALT or AST of at least 3 times the ULN have been reported in up to 2.5% of patients treated with sparsentan, that includes cases confirmed with rechallenge. It is noted that no concurrent elevations in bilirubin more than 2 time the ULN or cases of liver failure have been observed in patients treated with sparsentan in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, it is recommended to measure serum aminotransferase levels and total bilirubin prior to initiation of treatment, monthly for the first 12 months, then every 3 months during treatment. Patients should be advised of the symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) and to immediately stop treatment with sparsentan and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt treatment with sparsentan and monitor as recommended. Re-initiation of treatment should be considered only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity. Avoid initiation of sparsentan in patients with elevated

aminotransferases (greater than 3 times the ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

- Embryo-Fetal Toxicity: based on data from animal reproduction studies, sparsentan can cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Patients who can become pregnant should be advised of the potential risk to a fetus. As noted in the Boxed Warning, obtain a pregnancy test prior to initiation of sparsentan, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with sparsentan.
- FILSPARI REMS: due to the risk of hepatotoxicity and embryo-fetal toxicity, sparsentan is only available through a restricted program called the FILSPARI REMS. Important requirements of the FILSPARI REMS include the following:
  - Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
  - All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
  - Pharmacies that dispense sparsentan must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive sparsentan.
  - Further information is available at www.filsparirems.com or 1-833-513-1325.
- Hypotension: hypotension has been observed in patients treated with ARBs and ERAs and was observed in clinical studies with sparsentan. A greater incidence of hypotension related adverse events, some serious, including dizziness, was seen in patients treated with sparsentan compared to irbesartan in the PROTECT trial. It is recommended that in patients at risk for hypotension, to consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status. If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of sparsentan. It is noted that a transient hypotensive response is not a contraindication to further dosing of sparsentan, which can be given once blood pressure has stabilized.
- Acute Kidney Injury: it is recommended to periodically monitor kidney function in patients taking sparsentan. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., 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 sparsentan. It is recommended to consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on sparsentan.
- Hyperkalemia: it is recommended to periodically monitor serum potassium in patients prescribed sparsentan and to treat appropriately. Patients with advanced kidney disease or taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of sparsentan may be required.
- Fluid Retention: fluid retention may occur with ERAs and has been observed in clinical studies with sparsentan. Sparsentan has not been evaluated in patients with heart failure. It is recommended that if clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or adjust the dose of diuretic treatment then consider modifying the dose of sparsentan.

Other Considerations[1,2]

- The clinical trial in support of sparsentan's accelerated approval in patients with IgAN is currently ongoing and pending publication. An interim analysis on the reduction in proteinuria has recently been published. Per the prescribing information, the limitation of use notes that FDA approval is based on reduction in proteinuria. Whether sparsentan slows kidney function decline has yet to be established. Continued approval may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.
- The following drug interactions are noted with sparsentan (refer to the prescribing information for additional information):
  - Renin-Angiotensin System (RAS) inhibitors and ERAs: Contraindicated. Do not coadminister sparsentan with ARBs, ERAs, or aliskiren. Increased risk of hypotension, hyperkalemia.
  - Strong CYP3A inhibitors: Avoid concomitant use. Increased sparsentan exposure.

- Moderate CYP3A inhibitors: Monitor adverse reactions. Increased sparsentan exposure.
- Strong CYP3A inducers: Avoid concomitant use. Decreased sparsentan exposure.
- Antacids: Avoid use within 2 hours before or after use of sparsentan. May decrease exposure to sparsentan.
- Acid reducing agents: Avoid concomitant use. May decrease exposure to sparsentan.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase (COX-2) inhibitors: Monitor for signs of worsening renal function. Increased risk of kidney injury.
- CYP2B6, 2C9, and 2C19 substrates: Monitor for efficacy of the concurrently administered substrates. Decreased exposure of these substrates.
- Sensitive P-gp and BCRP substrates: Avoid concomitant use. Increased exposure to substrates.
- Agents Increasing Serum Potassium: Increased risk of hyperkalemia, monitor serum potassium frequently.

Other Therapeutic Options[1,3-7]

Guidelines recommend optimized supportive care (i.e., lifestyle intervention, including dietary sodium restriction, smoking cessation, weight control, exercise, as indicated) in all patients with IgAN, including blood pressure control. In patients with IgAN and proteinuria (> 0.5 g/d), treatment with an ACEI or ARB is recommended, regardless of history of hypertension. Glucocorticoid therapy is suggested for patients who remain at high risk of progressive CKD despite maximal supportive care. Table 4 includes sparsentan along with other selected medication treatment options for IgAN. Other therapies for consideration include: mycophenolate mofetil, hydroxychloroquine, SGLT2 inhibitor.

Table 4: Selected Treatment Options for IgAN[1,3-6]

Drug	Formulary status	FDA Approval and Guideline Recommendations
Endothelin and angiotensin II receptor antagonist		
sparsentan	Non-formulary	FDA indication to reduce proteinuria in primary IgAN at risk of rapid disease progression, generally a UPCR ≥ 1.5 g/g. The indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether sparsentan 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.
ACEI or ARB		
ACEI: e.g., lisinopril **ARB: e.g., irbesartan, losartan**	VA National Formulary	KDIGO Guideline Recommendation (Strong): Recommend all patients with proteinuria > 0.5 g/d, irrespective of hypertension, be treated with an ACEI or ARB (B: Moderate quality of evidence). Irbesartan included in clinical trial vs. sparsentan
Glucocorticoid		
methylprednisolone	VA National Formulary	KDIGO Guideline Recommendation (Weak): Suggest patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR < 50 ml/min/1.73 m2 (B: Moderate quality of evidence). Reduced doses of oral methylprednisolone (combined with antibiotic prophylaxis) may decrease the risk of end-stage kidney disease in patients with IgAN without the serious adverse events compared to higher dose methylprednisolone.
budesonide (capsule, delayed release)	Non-formulary	FDA indication to reduce proteinuria in primary IgAN at risk of rapid disease progression, generally a UPCR ≥ 1.5 g/g. The indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether the product 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.

Projected Place in Therapy[1-7]

- The majority of glomerular diseases are considered rare diseases, with IgAN as the most common primary glomerular disease. IgAN is typically an asymptomatic, slowly progressive condition, with interventions including supportive care and other therapies to slow the rate of progression of kidney disease. Treatment guidelines recommend an ACEI or ARB in patients with proteinuria (> 0.5 g/24 hours) [1B]. It is suggested that patients who remain at high risk of CKD progression despite supportive care be considered for a 6-month course of glucocorticoid therapy, with discussion of risk of treatment-emergent toxicity, especially in patients with an eGFR < 50 ml/min/1.73m2 [2B].[3]
- Sparsentan is an endothelin and angiotensin II receptor antagonist FDA approved to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥ 1.5 g/g. The indication is approved under accelerated approval based on reduction of proteinuria, that was demonstrated in patients with IgAN and proteinuria $\geq$ 1 g/day where there was a significant difference in the change from baseline in proteinuria at week 36 in patients treated with sparsentan compared to irbesartan. Whether sparsentan slows kidney function decline in patients with IgAN are pending clinical trial completion of the secondary outcome measures of rate of change in eGFR over a 52-week period. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial. Prescribing information for sparsentan includes a Boxed Warning due to the risks of hepatotoxicity and birth defects and is available only through a restricted use program (FILSPARI REMS). Additional warnings and precautions include hypotension, acute kidney injury, hyperkalemia, fluid retention, as well as several drug interactions.
- The place in therapy of sparsentan in IgAN is not yet established as only limited data are available for the surrogate outcome of reduction in proteinuria. Without published data as to the long-term safety and clinical outcome benefit, determination of whether treatment with sparsentan would provide benefit in a patient who remains at high risk of progressive CKD despite maximal supportive care, including treatment with an ACEI or ARB, and other guideline recommended therapies (e.g., limited course of glucocorticoid therapy, with more recent data on reduced dose therapy) should be evaluated on a case-by-case basis, taking into consideration other alternate therapies, the current lack of data for sparsentan in slowing kidney function decline, as well as the drug's safety including drug interactions and REMS program, and cost of therapy.

References

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