New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Filspari™ (sparsentan) [Travere Therapeutics, Inc.]** (fil-SPAR-ree)
Dosage Formulations:	Tablet (200 mg, 400 mg)
FDA Approval Date: **FDB File Date:**	FDA: February 17, 2023 FDB: February 27, 2023
Indication:	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. It was granted accelerated approval by the FDA on February 17, 2023.
Mechanism of Action:	Filspari is a Dual Endothelin Angiotensin Receptor Antagonist (DEARA) that selectively targets the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R), interfering with both pathways. In forms of a rare chronic kidney disease, it reduces proteinuria, protects podocytes and prevents glomerulosclerosis and cell proliferation.
Dose/ Administration:	• Dosing: ○ Initiate treatment at 200 mg orally once daily. After 14 days, increase to the recommended dose of 400 mg once daily. • Administration: ○ Prior to initiating treatment, discontinue use of renin–angiotensin-aldosterone-system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), and aliskiren due to risks of hyperkalemia and hypotension. ○ Tablet must be swallowed whole with water prior to the morning or evening meal. • Monitoring: ○ ALT, AST, and bilirubin should be measured at baseline. Filspari should not be initiated if ALT or AST are >3 times the upper limit of normal. ○ Continue 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. ○ A negative pregnancy test in patients who may become pregnant is required prior to Filspari treatment. Pregnancy testing is then required monthly during treatment and one month after the last dose of Filspari. ○ Periodic monitoring of blood pressure, serum creatinine, serum potassium, and fluid retention is recommended.
Disease State Clinical Highlights:	• IgA nephropathy is a form of glomerulonephritis in which antibodies build up in renal tissue. It has an incidence of 2.5 per 100,000 population per year and is estimated that approximately 150,000 people in the U.S. have this disease. IgAN can only be diagnosed with a kidney biopsy. • There are no validated diagnostic serum or urine biomarkers for IgAN • eGFR and proteinuria for the only biomarkers for IgAN prognosis • A urine protein-to-creatinine ratio (UPCR) can also be utilized to predict disease progression, with a UPCR ≥1.5 g/g indicating potential for rapid progression • Proteinuria is a standard measure of disease activity, which predicts and contributes to disease progression in IgAN

Degree of proteinuria	Normal to mildly increased	Moderately increased	Severely increased
Spot albuminuria to creatinine ratio (ACR)	<30 mg/g	30-299 mg/g	≥300 mg/g

Spot proteinuria to creatinine ratio (PCR)	<150 mg/g	150-499 mg/g	≥500 mg/g
Urine protein dipstick	Negative to trace	Trace to +	+ or greater

- Management of IgAN usually involves optimized supportive care, and immunosuppressive drugs are considered when patients have a risk of progressive chronic kidney disease (CKD). Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs) are commonly used to manage hypertension relative to glomerular disease and for proteinuria >0.5 g/d.
- IgA nephropathy is considered one of the most challenging kidney disease to manage.
    - Only 19% of IgAN patients are optimally managed.
    - Reasons for IgAN being challenging to manage includes provider's knowledge gaps, particularly regarding its etiology, the genetic factors, specific therapy for this disease, and the problem of recurrent disease in renal transplant recipients.
    - Non-specific symptoms complicate IgAN diagnosis. For instance, low-grade fever, hematuria, and back pain may be mistaken for a urinary tract infection or urolithiasis.

Drug Clinical Highlights:

- Filspari is a first-in-class molecule designed to selectively inhibit the Endothelin Receptor and Angiotensin II Receptor; it is also the second FDA-approved but first and only non-immunosuppressive therapy approved for IgAN. It was granted accelerated approval by the FDA for its significant reduction in proteinuria compared with ARBs. Continued approval for this indication and approval for the use focal segmental glomerulosclerosis may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- Warnings and Precautions: Hepatotoxicity
    - Filspari should be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.
    - If aminotransferase levels increase, adjust monitoring and treatment plan according to the table below:

ALT/AST	Recommendations
>3x and ≤8x ULN	Confirm elevation with a repeat measure. If confirmed, stop 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. Do not resume treatment if any of the following occurs without other cause found: • ALT or AST >3x ULN and total bilirubin >2x ULN or INR >1.5 • ALT or AST >3x ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia • ALT or AST >5x ULN for more than 2 weeks If treatment is resumed, initiate Filspari at 200 mg once daily, with reassessment of hepatic enzyme levels and bilirubin within 3 days.
>8x ULN	Stop treatment permanently if no other cause is found.

- Warnings and Precautions: Embryo-Fetal Toxicity
    - Filspari can cause major birth defects if used by pregnant patients based on animal data and is contraindicated in pregnancy.
    - A negative pregnancy test in patients who may become pregnant is required prior to Filspari treatment. Pregnancy testing is then required monthly during treatment and one month after the last dose of Filspari.
    - Patients should be advised to use effective contraception prior to initiation of Filspari, during treatment, and for one month after discontinuation of treatment

- Filspari Risk Evaluation and Mitigation Strategies (REMS)
    - Because of the risks of hepatotoxicity and embryo-fetal toxicity, Filspari is available only through a restricted program called the Filspari REMS.
    - Prescribers, patients, and pharmacies must enroll in the program.
- Prescribers should complete a prescriber enrollment form and acknowledge and understand the risks of Filspari and agree to comply with the requirements of the REMS program.
- Prescribers must enroll patients into the REMS program by having the patient submit the Patient Enrollment Form online or via fax.
- Patients who can become pregnant should undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.
- To become certified to dispense Filspari, a pharmacy must:
    - Designate an authorized representative to oversee implementation and compliance with the REMS program on behalf of the pharmacy.
    - Complete an online enrollment form
    - Counsel the patient on the potential adverse effects of Filspari, and verify completion of laboratory results related to LFTs and reproductive status

- Adverse Reactions (≥ 5%):
    - Peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.
- Drug Interactions
    - Avoid concomitant use of strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with Filspari.
    - Do not coadminister Filspari with ACE-I, ARBs, ERAs, or aliskiren, as this can increase the risk of hypotension, syncope, hyperkalemia, and changes in renal function.
    - Filspari has pH-dependent solubility, therefore should be administered 2 hours before or after antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor).
    - Monitor for signs of worsening renal function with concomitant use of NSAIDs
    - Filspari is an inducer of CYP2B6, 2C9, and 2C19; monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment.
    - Filspari is an inhibitor of P-gp and BCRP; avoid concomitant use of sensitive substrates of P-gp and BCRP.
    - Monitor serum potassium frequently in patients treated with Filspari and other agents that increase serum potassium, Concomitant use of Filspari with agents that increase potassium can cause hyperkalemia.

- Clinical Studies: PROTECT (NCT 03762850)
    - Phase 3, randomized, double-blind, active-controlled, multicenter trial.
    - Inclusion criteria:
        - biopsy-proven IgAN
        - eGFR ≥30 mL/min/1.73 m2
        - Total urine protein ≥1.0 g/day on a maximized stable dose of a RAAS inhibitor treatment that was at least 50% of the maximum labeled dose.
    - Patients were randomized (1:1) to either:
        - Filspari (400 mg once daily following 200 mg once daily for 14 days)
        - Irbesartan (300 mg once daily following 150 mg once daily for 14 days).
    - Baseline Demographics:
        - 281 patients who reached week 36 had a mean age of 46 years (range 18 to 76 years)
        - 69% were male
        - 62% white

- 35% Asian
- 1% black or African American
- ~77% had history of hypertension
- 12% had history of diabetes or impaired fasting glucose
- 53% had hematuria.
- Mean baseline eGFR: 56 (24) mL/min/1.73 m2.

- Primary Outcome: The relative change from baseline in UPCR at Week 36.

PROTECT (NCT 03762850)	Filspari (N=141)	Irbesartan (N=140)
Adjusted GM (Geometric Mean) of UPCR, g/g		
Baseline	1.2 (n=141)	1.2 (n=140)
Week 36	0.7 (n=135)	1.0 (n=128)
Adjusted GM % Change from baseline in UPCR at week 36 (95% CI)	-45% (-51%, -38%)	-15% (-24%, -4%)
Filspari versus Irbesartan: Ratio of adjusted GM relative to baseline at week 36 (95% CI)	0.65 (0.55, 0.77)	
p-value	<0.0001	

- Adverse Events:

	Filspari (N = 202) n (%)	Irbesartan (N = 202) n (%)
Peripheral edema	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury	9 (4)	2 (1)
Transaminase elevations	5 (2.5)	4 (2)

- Laboratory Tests:
  - Initiation of Filspari may cause an initial small decrease in estimated glomerular filtration rate (eGFR) within the first 4 weeks of starting therapy and then will stabilize.

Price Per Unit (WAC):

$120,450 annually.
$330.00 per tab ($9,900 per 30 count bottle)

Therapeutic Alternatives:

- The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, recommends initial therapy with an ACEI or ARB for patients with proteinuria >0.5 g per day, regardless of whether the patient has hypertension.
- SGLT2 inhibitors may also be added to this regimen based on data from the DAPA-CKD trial (NCT 03036150).
- Currently, the only FDA-approved treatment for IgAN is Tarpeyo, a 505(b)(2) corticosteroid indicated to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression. Tarpeyo was granted accelerated approval by the FDA in December 2021. Filspari is the only non-immunosuppressive therapy indicated for IgAN.
- Irbesartan is known to have off-label use in proteinuric chronic kidney disease. It acts to inhibit angiotensin II receptor type 1 (AT1) only without affecting the endothelin receptor.
- A Phase 2 trial study (DUET trial; NCT 01613118) compared Filspari (at all doses) with Irbesartan 300 mg to evaluate effect on urine protein:serum creatinine ratio.
  - Irbesartan reduced urine protein:serum creatinine ratio by 18.5% from baseline.
  - Filspari reduced urine protein:serum creatinine ratio by 44.8% from baseline.
  - There was a significant reduction in proteinuria after 8 weeks of Filspari vs irbesartan treatment in primary and genetic FSGS patients only.

	Avapro®	Filspari™

	(Irbesartan)	(Sparsentan)
Therapeutic Class	Angiotensin receptor blocker	Endothelin and Angiotensin Receptor Antagonist
FDA Approval	September 17, 2002	February 17, 2023
Mechanism of Action	Angiotensin II inhibition	Angiotensin II/Endothelin receptor inhibition
Route of Administration	Oral	Oral
Maintenance Dose	150 to 300 mg once daily	200 mg once daily for 14 days, increase to 400 mg once daily

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with an appropriate specialist in the treated disease state **AND**
- Documented diagnosis of IgAN as verified by kidney biopsy **AND**
- UPCR ≥ 1.5 **AND**
- eGFR ≥ 30 mL/min/1.73 m^2 **AND**
- Participant is ≥ 18 years of age **AND**
- Participant is currently not pregnant **AND**
- Documented therapeutic trial of an ACEI or ARB at a maximally tolerated dose for at least 6 months of therapy

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Optimal monitoring of the participant's liver function with Filspari therapy.
  - 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 3x ULN every 3 months during treatment.
  - Avoid use in participants with elevated aminotransferases (>3x ULN) at baseline to avoid risk of worsening hepatotoxicity.
- REMS Criteria
  - Prescriber, participant, and pharmacy are all enrolled in the REMS program
  - Participant is currently not pregnant **AND**
  - Participant is utilizing concurrent effective contraception methods if applicable **AND**
  - Participant's LFTs are being monitored and are WNL based on manufacturer's recommendations

Implication to State Medicaid Program:

LOE: 2030-2039

There is not currently a specific ICD10 code for IgAN. IgAN and similar disorders may fall under "Recurrent and persistent hematuria with other morphologic changes (N02.8)"

Other Studies:

EPPIK (NCT05003986) – A Phase 2, multicenter study that studies the safety, efficacy, and pharmacokinetics (PK) of Filspari in pediatrics over 108 weeks. Estimated study completion is June 2025.

DUPLEX (NCT03493685) – A Phase 3, randomized, multicenter, double-blind, parallel, active-control study. This study determines the long-term nephroprotective potential of treatment with Filspari as compared to an angiotensin receptor blocker in patients with primary and genetic focal segmental glomerulosclerosis (FSGS) that determine the long-term effect of Filspari in FSGS patients. Estimated study completion is February 2026.

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