Atrasentan (VANRAFIA) in IgA Nephropathy
National Drug Mini-monograph
November 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION	
Description / MOA	Endothelin type A (ETA) receptor antagonist
Indication Under Review[1]	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. This indication is approved under accelerated approval based on a reduction in proteinuria. It has not been established whether atrasentan slows kidney function decline in patients with IgAN. Continued approval may be contingent upon verification of clinical benefit in a confirmatory trial.
Dosage Regimen	0.75 mg taken orally once daily, with or without food.
Dosage Forms Under Review	Tablets: 0.75 mg

EFFICACY CONSIDERATIONS	
Trial	**Atrasentan in Patients with IgA Nephropathy (ALIGN)**
Design	A phase 3, multinational, double-blind, randomized, placebo-controlled trial. Randomization was 1:1. This report is based on a prespecified interim analysis.
Population	Adults (≥18 years of age) with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2. Patients were required to be on a stable, maximum tolerated dose of an ACE inhibitor or an ARB for at least 12 weeks before screening. Key exclusion criteria included secondary IgA nephropathy or a history of heart failure.
Baseline Characteristics	In the first 270 patients, the mean age was 44.9 years, 58.9% were men, and the mean eGFR was 58.9 ml/min/1.73 m^2. The median 24-hour urinary protein-to-creatinine ratio was 1433. The majority of patients were Asian (57.0%) or White (35.9%). Nearly all patients (98.5%) were using an ACE inhibitor or ARB at baseline.
Intervention	Atrasentan 0.75 mg once daily added to supportive care (maximally tolerated RAS inhibitor).
Comparator	Placebo once daily added to supportive care (maximally tolerated RAS inhibitor).
Results	Primary Endpoint: change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36, based on the first 270 patients in the main stratum. At week 36, the geometric mean percentage change in the urinary protein-to-creatinine ratio from baseline was -38.1% in the atrasentan group (N=124) compared to -3.1% in the placebo group (N=114). This resulted in a statistically significant geometric mean between-group difference of -36.1 percentage points (P<0.001). The reduction in proteinuria with atrasentan was observed as early as week 6 and was sustained through week 36.

SAFETY CONSIDERATIONS	
Boxed Warnings	Embryo-fetal toxicity: Atrasentan may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting treatment. Effective contraception is required before, during, and for two weeks after treatment. Discontinue if pregnancy occurs.
Contraindications	Pregnancy Hypersensitivity to atrasentan or any component of the product.
Other Warnings	Hepatotoxicity: Some endothelin receptor antagonists (ERAs) have caused liver enzyme elevations, hepatotoxicity, and liver failure. Liver enzyme testing should be done before and during treatment as clinically indicated. Fluid Retention: Fluid retention can occur with ERAs and was observed in clinical studies with atrasentan. It was reported in 11.2% of patients on atrasentan versus 8.2% on placebo in the ALIGN trial. If clinically significant fluid retention occurs, consider diuretic use and interrupting atrasentan. Decreased Sperm Counts: Atrasentan may adversely affect spermatogenesis. Men should be counseled about potential effects on fertility.
Top 5 AEs	Nasopharyngitis (10.1%), Peripheral edema (10%), Anemia (6.5%), Pyrexia (6.5%), Upper respiratory tract infection (6.5%)

Drug Interactions

Strong or moderate CYP3A inducers**:** Avoid concomitant use as they may decrease atrasentan exposure and efficacy.

OATP1B1/1B3 inhibitors: Avoid concomitant use as they may increase atrasentan exposure and the risk of adverse reactions.

PLACE IN THERAPY

DRUG	VANF	CFU	Mechanism	Considerations
Atrasentan (VANRAFIA)	TBD	TBD	Selective endothelin A receptor antagonist	Add on therapy to RAS inhibitors; Reduces proteinuria; risk of fluid retention
RAS inhibitors (ACEi/ARB)	Yes	No	RAAS blockade	First-line; reduces proteinuria; monitor for hyperkalemia, AKI
SGLT2 inhibitors (empagliflozin)	Yes	No	SGLT2 inhibition	Add on therapy to RAS inhibitors; Reduces proteinuria; slows CKD progression; low risk of hypoglycemia
Sparsentan (FILSPARI)	No	No	Dual endothelin A/angiotensin II receptor antagonist	Replaces RAS inhibitors; Reduces proteinuria; slows eGFR decline; risk of hypotension, edema
Iptacopan (FABHALTA)	No	No	Complement factor B inhibitor	Add on therapy to RAS inhibitors; Reduces proteinuria; favorable safety profile; ongoing eGFR data
Targeted-release Budesonide (TARPEYO)	No	No	Glucocorticoid (local ileal release)	Add on therapy to RAS inhibitors; Reduces proteinuria; modest eGFR benefit; risk of steroid toxicity

VHA PLACE IN THERAPY

Potential Use in VHA

- IgA nephropathy is the most common primary glomerular disease and carries a substantial lifetime risk of kidney failure.
- The current best practice for management of IgA nephropathy is grounded in the KDIGO guideline framework, which emphasizes maximally tolerated renin-angiotensin system (RAS) inhibition and comprehensive supportive care as the foundation of therapy for all patients at risk of progression. For those with persistent proteinuria despite optimized RAS blockade, additional interventions such as SGLT2 inhibitors and, in select high-risk cases, immunosuppression may be considered.
- Atrasentan is FDA-approved to reduce proteinuria in adults with primary IgA nephropathy (IgAN) at risk of rapid progression (UPCR ≥ 1.5 g/g), as add-on to maximally tolerated RAS inhibition.
- Atrasentan may be considered as an adjunct to maximally tolerated RAS inhibition in adults with primary IgA nephropathy and persistent proteinuria (generally UPCR ≥1.5 g/g), particularly in patients at high risk for progression and prior to or as an alternative to immunosuppression (considering efficacy in reducing proteinuria and its favorable safety profile).
- Current formulary options include RAS inhibitors and SGLT2 inhibitors (empagliflozin).
- The greatest uncertainties surrounding atrasentan as an intervention for IgA nephropathy include the lack of long-term data on its effect on hard renal outcomes such as kidney failure, its optimal sequencing or combination with other disease-modifying therapies (e.g., SGLT2 inhibitors, corticosteroids), and the generalizability of trial results to broader or lower-risk patient populations. Atrasentan could be considered as an add-on therapy for adult VHA patients with primary IgA nephropathy who have persistent proteinuria (≥1 g/day) despite being on a maximally tolerated dose of a RAS inhibitor and failure of other agents.

References

1 VANRAFIA (atrasentan) tablets [prescribing information online]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. April 2025. Available at: https://www.novartis.com/us-en/sites/novartis_us/files/vanrafia.pdf. Accessed September 5, 2025.

2 Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in Patients with IgA Nephropathy. *N Engl J Med*. 2025;392(6):544-554. doi:10.1056/NEJMoa2409415

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