IOWA | Health and Human Services

Iowa PDL New Drug Review

Proprietary Name: Vanrafia®
Common Name: atrasentan
PDL Category: Endothelin Receptor Antagonists

Pharmacology/Usage: Atrasentan, the active ingredient of Vanrafia®, is an endothelin type A (ETA) receptor antagonist. It has >1800-fold selectivity for the ETA receptor compared to the endothelin type B receptor. Endothelin (ET)-1 is thought to contribute to the pathogenesis of immunoglobulin A nephropathy (IgAN) via the ETA receptor.

Indication: To reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5g/g.

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

There is no pregnancy category for this medication; however, the risk summary indicates that based on data from animal reproductive toxicity studies, Vanrafia® may cause fetal harm, including birth defects and fetal death, when given to a pregnant patient, and is contraindicated during pregnancy. There are no available data on use in pregnancy to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Advise pregnant patients of the potential risk to a fetus. Exclude pregnancy before starting treatment in females of reproductive potential. If pregnancy is confirmed, the physician should discuss with the patient the risks to the pregnancy and the fetus. Patients who can become pregnant while using Vanrafia® should use effective contraception prior to the start of treatment, during treatment, and for two weeks after discontinuation of treatment. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 0.75mg

Recommended Dosage: Exclude pregnancy before starting Vanrafia®.

Take 0.75mg PO QD with or without food. Swallow tablets whole; do not cut, crush, or chew.

If a dose or doses are missed, take the prescribed dose at the next scheduled time. Do not double the dose to make up for a missed dose.

Dose adjustments are not required for patients with mild or moderate hepatic impairment; however, do not initiate Vanrafia® in patients with severe hepatic impairment.

Drug Interactions: Atrasentan is a CYP3A substrate. Avoid concomitant use of Vanrafia® with a strong or moderate CYP3A inducer.

Atrasentan is an organic anion transporting polypeptides 1B1/1B3 (OATP1B1/1B3) substrate. Avoid concomitant use of Vanrafia® with OATP1B1/1B3 inhibitors.

Box Warning: This product has a box warning regarding embryo-fetal toxicity. Vanrafia® is contraindicated for use in pregnant patients; it may cause major birth defects based on animal data. Exclude pregnancy prior to initiation of Vanrafia® treatment. Advise use of effective contraception before the start of treatment, during treatment, and for two weeks after discontinuation of treatment with Vanrafia®. Stop Vanrafia® as soon as possible if the patient becomes pregnant.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Vanrafia®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included peripheral edema (3%), anemia (5%), and liver transaminase elevation (1%).

Some endothelin receptor antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. Asymptomatic and transient transaminase elevations have been observed with Vanrafia®. Obtain liver enzyme testing before starting treatment and repeat during treatment as clinically indicated. In patients with elevated aminotransferases at baseline (>3 X upper limit of normal [ULN]), consider periodic liver test monitoring. Do not start Vanrafia® in patients with severe hepatic impairment. Advise patients to report symptoms suggesting hepatic injury. If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 X ULN, or by clinical symptoms of hepatotoxicity, discontinue Vanrafia®. Consider re-initiation of Vanrafia® when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity or jaundice.

Fluid retention may occur with ERAs and has been observed in clinical studies with Vanrafia®. Vanrafia® has not been assessed in IgAN patients with heart failure. If clinically significant fluid retention develops, consider initiating or increasing diuretic treatment and interrupting Vanrafia® treatment.

Vanrafia®, similar to other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

Contraindications: In patients:

- Who are pregnant.
- With a history of a hypersensitivity reaction to atrasentan or any component of the product.

Manufacturer: Novartis Pharmaceuticals Corporation

Analysis: The effect of Vanrafia® on proteinuria was assessed in a randomized, double-blind, placebo-controlled, multicenter study (ALIGN) that included adults with biopsy-proven primary IgAN, an eGFR ≥30ml/min/1.73m^2, and urine protein ≥1g/day on a stable dose of maximally tolerated renin angiotensin system (RAS) inhibitor. Two cohorts were included in the study: a main cohort (N=340) and an exploratory cohort (N=64) who were also on a stable dose of sodium glucose co-transporter 2 inhibitor (SGLT2 inhibitor) at baseline. Patients with chronic kidney disease due to another condition in addition to IgAN or those who had been recently treated with systemic immunosuppressants were excluded.

During the study, patients were randomized to receive either Vanrafia® or placebo, while RAS inhibitor therapy was continued throughout the study. In addition, rescue immunosuppressive treatment could be started per investigator discretion during the trial. The efficacy analysis included the first 270 patients in the main cohort who reached the week 36 visit. At baseline, the mean age of patients was 45 years (range 19 to 77), while 59% were male, 36% were white, 60% had a history of hypertension, 1.5% had a history of type 2 diabetes, and 45% had hematuria based on urine dipstick. The mean baseline eGFR was 59ml/min/1.73m^2, the geometric mean baseline urine protein-to-creatinine ratio (UPCR) was 1.5g/g sampled from a 24-hour urine, and 15% had proteinuria >3.5g/day.

The primary endpoint was the percent reduction in UPCR at week 36 relative to baseline. Results are presented in the table below, which was adapted from the prescribing information. Reminder that in both groups, randomized

treatment was on top of supportive care (supportive care- primarily a stable dose of maximally-tolerated RAS inhibitor therapy).

Endpoint	Vanrafia® (N=135)	Placebo (N=135)
% reduction in UPCR at week 36 relative to baseline	38%	3%
Vanrafia® vs placebo: % reduction in UPCR at week 36 relative to baseline compared on a relative scale; p-value	36%; p<0.0001	

The treatment effect on UPCR at week 36 was consistent across subgroups including age, sex, race, and baseline disease characteristics within the main cohort. The treatment effect on UPCR at week 36 was also consistent in the exploratory SGLT2 inhibitor cohort.

Place in Therapy: Vanrafia® is an endothelin 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) ≥1.5g/g. This indication is approved under accelerated approval based on a reduction of proteinuria. It has not been established whether Vanrafia® 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. It has a box warning regarding embryo-fetal toxicity, as it may cause major birth defects if used during pregnancy. Exclude pregnancy prior to the start of treatment. In addition, use effective contraception before the start of treatment, during treatment, and for two weeks after treatment discontinuation. If pregnancy occurs, discontinue Vanrafia®. The efficacy of Vanrafia® was assessed in a randomized, double-blind, placebo-controlled study that included adults with biopsy-proven primary IgAN, an eGFR ≥30ml/min/1.73m^2, and urine protein ≥1g/day on a stable dose of maximally tolerated renin angiotensin system inhibitor. The primary endpoint was the percent reduction in UPCR at week 36 relative to baseline, and results suggested that Vanrafia® had a statistically significant greater percentage reduction in UPCR at week 36 as compared with placebo (p<0.0001; NNT 3). Generally, supportive care, including blood pressure control and reduction of proteinuria with renin-angiotensin system inhibition, as well as treatment of dyslipidemia and lifestyle modification, is the initial management of primary IgAN. If proteinuria persists even with ACE inhibitor or ABR treatment, then it is suggested to add an SGLT2 inhibitor, an ERA (atrasentan), or sparsentan.[2] Vanrafia® is a selective endothelin type A receptor antagonist that provides another treatment option to be added to supportive care.

Summary

There is no evidence to suggest that Vanrafia® is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Vanrafia® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Vanrafia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2025.
[2] UpToDate online. IgA nephropathy: Treatment and prognosis. Accessed June 2025.