Drug Coverage Policy

Effective Date.....11/1/2025
Coverage Policy Number.....IP0740
Policy Title.....Vanrafia

Nephrology – Vanrafia

- Vanrafia™ (atrasentan tablets - Novartis)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

Vanrafia, an endothelin receptor antagonist, is indicated to reduce proteinuria in adults with **primary immunoglobulin A nephropathy** (IgAN) who are at risk of rapid disease progression, generally a urine protein-to-creatinine ration (UPCR) ≥ 1.5 g/g.[1]

Vanrafia was approved under accelerated approval based on reduction of proteinuria.[1] 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.

Disease Overview
IgAN is the most common primary glomerular disease in the world, and it is the leading cause of chronic kidney disease (CKD) and kidney failure.[2] The disease is slowly progressive; approximately 25% to 30% of patients develop kidney failure within 20 to 25 years of presentation. The management of IgAN is focused on supportive care to slow the rate of disease progression. IgAN is characterized by a single histopathologic criterion of predominant or co-dominant IgA deposits on kidney biopsy; however, it is well recognized that the disease exhibits heterogeneity in clinical and pathological features. Hypertension and proteinuria are major risk factors for the progression of CKD. Guidelines from Kidney Diseases: Improving Global Outcomes (KDIGO) [2024] note that proteinuria reduction to < 0.5 g/day, a surrogate marker of improved kidney outcomes in IgAN, is a reasonable target.

Clinical Efficacy
The efficacy of Vanrafia was evaluated in a Phase III trial in adults with biopsy-proven IgAN, proteinuria ≥ 1.0 g/day at screening, and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 (ALIGN, n = 270).[1,3] Additionally, patients were receiving the maximum tolerated dose of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for ≥ 12 weeks prior to study entry. Patients with use of immunosuppressive medications (including corticosteroids for > 2 weeks within 3 months of screening), chronic kidney disease (CKD) in addition to IgAN, or IgAN secondary to other conditions were excluded. The majority of patients remained on a renin-angiotensin system inhibitor throughout the study.[1]

The primary efficacy endpoint was the change from baseline in urine protein-to-creatinine ratio (based on 24-hour urine sample) at Week 36.[1,3] At Week 36, the primary endpoint was significantly greater with Vanrafia in the interim analysis set (comprised of the first 270 patients randomized in the study, who completed 36 weeks of the trial). The geometric least squares mean percent change in UPCR from baseline was -38% for Vanrafia vs. -3% for placebo. This resulted in a statistically significant relative reduction from baseline in UPCR for the Vanrafia, corresponding to a 36% relative reduction with Vanrafia (P < 0.001). Exploratory efficacy endpoints for changes in UPCR from baseline to Week 36 in the sodium-glucose linked transporter (SGLT) 2 inhibitor stratum, was -39% for Vanrafia (14 patients) compared to -3% for placebo (15 patients).[3]

Safety
Vanrafia has a Black Box Warning for embryo-fetal toxicity.[1] Vanrafia may cause major birth defects if used during pregnancy. Effective contraception must be started before the start of treatment and continued for 2 weeks after treatment.

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Policy Statement
Prior Authorization is required for prescription benefit coverage of Vanrafia. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis

of patients treated with Vanrafia as well as the monitoring required for adverse events and long-term efficacy, approval requires Vanrafia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

Vanrafia is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Primary Immunoglobulin A Nephropathy.** Approve for 9 months if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy **[Documentation Required]**; AND
     - **iii.** Patient is at high risk of disease progression, defined by meeting BOTH of the following (a and b):
       - **a)** Patient meets ONE of the following [(1) or (2)]:
         (1) Proteinuria ≥ 0.5 g/day **[Documentation Required]**; OR
         (2) Urine protein-to-creatinine ratio ≥ 1.5 g/g **[Documentation Required]**; AND
       - **b)** Patient has received or is currently receiving the maximum or maximally tolerated dose of ONE of the following for ≥ 12 weeks prior to starting Vanrafia [(1) or (2)]:
         (1) Angiotensin converting enzyme inhibitor; OR
         (2) Angiotensin receptor blocker; AND
     - **iv.** According to the provider, patient has received ≥ 3 months of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification; AND
     - **v.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **vi.** The medication is prescribed by or on consultation with a nephrologist; OR
   - **B)** Patient is Currently Receiving Vanrafia. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy **[Documentation Required]**; AND
     - **iii.** According to the prescriber, patient has had a response to Vanrafia,; AND
       Note: Examples of a response are a reduction in urine protein-to-creatinine ratio from baseline, reduction in proteinuria from baseline.
     - **iv.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **v.** The medication is prescribed by or on consultation with a nephrologist.

Conditions Not Covered

Vanrafia for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as newly published data are available):

1. **Concurrent use with other medications indicated for the treatment of immunoglobulin A nephropathy (e.g., Fabhalta and Filspari).**

The requested medication should not be administered in combination with other medications indicated for immunoglobulin A nephropathy. Combination therapy is generally not recommended due to a lack of controlled clinical trial data supporting additive efficacy.

References

1. Vanrafia™ tablets [prescribing information]. East Hanover, NJ: Novartis; April 2025.
2. Kidney Diseases: Improving Global Outcomes (KDIGO) 2024 clinical practice guidelines for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). *Draft published online ahead of print.* Available at: https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf. Accessed on February 20, 2025.
3. Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in Patients with IgA Nephropathy. *N Engl J Med*. 2025;392(6):544-554.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy.	07/01/2025
Selected Revision	**Updated** policy template.	11/1/2025

The policy effective date is in force until updated or retired.