valoctocogene roxaparvovec-rvox (Roctavian™)

Medicare Advantage Medical Policy # 088
Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider valoctocogene roxaparvovec-rvox (Roctavian™)‡ for the treatment of hemophilia A to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of valoctocogene roxaparvovec-rvox (Roctavian) for the treatment of hemophilia A will be considered when ALL of the following patient selection criteria are met:

- Patient is 18 years of age or older; AND
- Patient has severe hemophilia A as defined by a baseline plasma Factor VIII level ≤ 1% of normal (< 1 IU/dL); AND
- Patient is currently receiving FVIII prophylaxis or emicizumab (Hemlibra®)‡ continuously for at least 12 months; AND
- Patient meets ONE of the following:
    - Patient has experienced a current or historical life-threatening hemorrhage (e.g., CNS hemorrhage) requiring treatment with on-demand Factor VIII infusion; OR
    - Patient has experienced repeated, serious spontaneous bleeding episodes requiring treatment with on-demand Factor VIII infusion (e.g., bleeds requiring hospitalization, recurrent spontaneous bleeds in a joint or deep muscle); AND
- Patient has received > 150 exposure days of treatment with Factor VIII protein; AND
- Provider agrees to discontinue prophylaxis following appropriate timeframe for Factor VIII levels to reach therapeutic levels after steady state after patient has received Roctavian; AND
- Patient does not have a history of Factor VIII inhibitors or a positive screen result of ≥ 0.6 Bethesda Units (BU) using the Nijmegen-Bethesda assay; AND
- Patient has received a liver health assessment including enzyme testing [ALT, AST, ALP, and total bilirubin] AND a hepatic ultrasound and elastography; AND
- There is no evidence of cirrhosis and liver function tests are all below two times the upper limit of normal (except for total bilirubin if caused by Gilbert syndrome); AND

- Patient does not have detectable pre-existing immunity to the AAV5 capsid as measured by the AAV5 transduction inhibition or AAV5 total antibodies (as detected by an FDA-approved companion diagnostic test [AAV5 DetectCDx]); AND
- Patient does not have a history of receiving any prior gene therapy and is not under consideration for treatment with another gene therapy for hemophilia A; AND
- Patient is HIV negative; AND
- Patient does NOT have an active hepatitis B and/or hepatitis C infection (i.e., negative HCV RNA and not currently using antiviral therapy for hepatitis B or C); AND
- Patient does NOT have a contraindication to the use of corticosteroids or immunosuppressants in the event that ALT levels are elevated post-infusion; AND
- Provider attests that the patient has been counseled regarding the risks of alcohol consumption and use of concomitant hepatotoxic medications after receiving Roctavian and the patient agrees to abstain from alcohol consumption for at least 1 year following infusion; AND
- Patient does not have a history of venous or arterial thrombosis (outside of catheter-associated thromboses) or known thrombophilia; AND
- Dose will not exceed one lifetime dose of 6×10^{13} vector genomes (vg) per kg based on current body weight (within the past 30 days) administered by IV infusion; AND
- All care, services, and administration of Roctavian will be provided by a federally designated hemophilia treatment center; AND
- Prescriber attests and agrees to provide the necessary clinical outcome information via the Value Based Administrator's (Evio) secure web portal for the purposes of tracking and monitoring patient medical status and treatment outcomes; AND
- Member attests and agrees to provide access to their current and/or future physician(s) rendering care for the condition associated with this drug therapy. The member agrees to allow this access by their physician, whether the member remains as a member with the Plan or is no longer a member with the Plan.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of valoctocogene roxaparvovec-rvox (Roctavian) when the following criteria are NOT met to be **not medically necessary.****

- Patient is currently receiving FVIII prophylaxis or emicizumab (Hemlibra) continuously for at least 12 months; AND
- Patient has received > 150 exposure days of treatment with Factor VIII protein; AND
- Provider agrees to discontinue prophylaxis following appropriate timeframe for FVIII levels to reach therapeutic levels after steady state after patient has received Roctavian; AND

- Patient does not have a history of receiving any prior gene therapy and is not under consideration for treatment with another gene therapy for hemophilia A; AND
- Patient is HIV negative; AND
- All care, services, and administration of Roctavian will be provided by a federally designated hemophilia treatment center; AND
- Prescriber attests and agrees to provide the necessary clinical outcome information via the Value Based Administrator's (Evio) secure web portal for the purposes of tracking and monitoring patient medical status and treatment outcomes; AND
- Member attests and agrees to provide access to their current and/or future physician(s) rendering care for the condition associated with this drug therapy. The member agrees to allow this access by their physician, whether the member remains as a member with the Plan or is no longer a member with the Plan.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of valoctocogene roxaparvovec-rvox (Roctavian) when the patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Roctavian is an adeno-associated virus vector-based gene therapy that is indicated for the treatment of adults with severe hemophilia A without antibodies to adeno-associated virus serotype 5. It is administered via a single intravenous infusion containing 6×10^{13} vector genomes per kilogram (vg/kg) body weight. It uses an adeno-associated virus (AAV5) to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII. Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in expression of the SQ form of human coagulation factor VIII. This expressed protein replaces the missing coagulation factor VIII needed for effective hemostasis.

Roctavian is contraindicated in patients with active infections (either acute or uncontrolled chronic), known significant hepatic fibrosis or cirrhosis, or known hypersensitivity to mannitol. Additionally, Roctavian is not intended for administration in females. Despite patients with liver function abnormalities being excluded from the clinical trial, the majority of patients in the trial required corticosteroids for ALT elevation with 18% requiring immunosuppression for greater than 1 year. The package insert also notes that some ALT elevations have been attributed to alcohol consumption

and that patients should abstain from alcohol consumption for at least a year following Roctavian infusion and limit alcohol use thereafter.

Hemophilia A is a bleeding disorder that is caused by a deficiency or dysfunction in clotting factor VIII, a protein that enables blood to clot. Because the disorder is transmitted on the X-chromosome, it primarily affects males. The incidence of hemophilia is one in every 5,000 males born in the United States, approximately 80% of whom have hemophilia A. the condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas (e.g., muscles, central nervous system, gastrointestinal). The bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated.

Disease severity is usually defined by plasma levels of factor VIII and has been classified as follows:

- Severe: levels less than 1% of normal
- Moderate: levels 1-5% of normal
- Mild: levels > 5% to 40% of normal

Approximately 25-30% of patients with hemophilia A have severe disease. The main treatment strategy for hemophilia A is factor VIII replacement therapy in which administration of the deficient clotting factor is given to achieve adequate hemostasis. Depending on individual patient characteristics such as disease severity and number of bleeds, patients may receive prophylactic factor VIII replacement therapy or only receive treatment in response to a bleed ("on demand therapy"). Many different factor VIII replacement therapies are FDA approved. An alternative to factor prophylaxis is emicizumab (Hemlibra), a bispecific factor IXa and factor X-directed antibody that is administered subcutaneously.

Evio has been selected to administer clinical outcomes monitoring for patients receiving certain high-cost drug therapies. This therapy is included in the portfolio of high-cost drug therapies for which Evio will be tracking clinical outcomes. If a patient meets all medical policy provisions and is approved to receive treatment, the requesting physician must attest and agree to providing clinical outcomes data and information via Evio's secure web portal as requested. In addition, the member must attest and agree to providing access to their current and/or future physician(s) rendering care for the condition associated with this drug therapy. The member agrees to allow this access by their physician, whether the member remains as member with the Plan or is no longer a member with the Plan.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Roctavian was approved in June 2023 for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA-approved test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Roctavian was evaluated in a prospective, phase 3, open-label, single-dose, single-arm, multinational study in 134 adult males with severe hemophilia A, who received a single intravenous dose of 6×10^{13} vg/kg body weight of Roctavian and entered a follow-up period of 5 years. Patients previously treated with prophylactic factor VIII replacement therapy, but not emicizumab (Hemlibra), were enrolled in the study. The median age was 30 (range: 18 to 70) years.

Only patients without detectable, pre-existing antibodies to AAV5 capsid (using AAV5 DetectCDx total antibody assay) were eligible for therapy. Other key exclusion criteria included active infection, chronic or active hepatitis B or C, immunosuppressive disorder including HIV, current or prior history of factor VIII inhibitor, stage 3 or 4 liver fibrosis, cirrhosis, liver function test abnormalities, history of thrombosis or thrombophilia, serum creatinine $\geq$ 1.4 mg/dL, and active malignancy.

Of the 134 patients who received Roctavian, 112 patients had baseline annualized bleeding rate (ABR) data prospectively collected during a period of at least 6 months on factor VIII prophylaxis prior to receiving Roctavian. The remaining 22 patients had baseline ABR collected retrospectively. All patients were followed for at least 3 years. The primary efficacy outcome was a non-inferiority test of the difference in ABR in the efficacy evaluation period (EEP) following Roctavian administration compared with ABR during the baseline period in the rollover population. The noninferiority margin was 3.5 bleeds per year. All bleeding episodes, regardless of treatment, were counted towards ABR. The EEP started from Study Day 33 (Week 5) or the end of factor VIII prophylaxis including a washout period after Roctavian treatment, whichever was later, and ended when a patient completed the study, had the last visit, or withdrew or was lost to follow-up from the study, whichever was earliest. At a median of 3 years of follow up, the mean ABR was 2.6 bleeds per year, compared to a mean baseline ABR of 5.4 bleeds per year. The mean difference in ABR

was -2.8 (95% CI: -4.3, -1.2) bleeds per year. The noninferiority analysis met the pre-specified noninferiority margin, indicating the effectiveness of Roctavian.

A majority of patients treated with Roctavian received immunosuppressive medications, including steroids, to control elevations in transaminases and to prevent loss of transgene expression.

In the rollover population, a total of 5 patients (4%) did not respond and 17 patients (15%) lost response to Roctavian treatment over a median time of 2.3 (range: 1.0 to 3.3) years. In the directly enrolled population with a longer follow-up, a total of 1 patient (5%) did not respond and 6 patients (27%) lost response to Roctavian treatment over a median time of 3.6 (range: 1.2 to 4.3) years.

References

1. Roctavian [package insert]. BioMarin Pharmaceuticals, Inc. Novato, CA. Updated June 2023.
2. Roctavian New Drug Review. IPD Analytics. Updated August 2023.
3. Hemlibra Drug Evaluation. Express Scripts. Updated January 2018.

Policy History

Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025
02/18/2025 UM Committee Review. New Policy
Next Scheduled Review Date: 02/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which

contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No Codes
HCPCS	J1412
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.