Policy Number	**RX501.128**
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Valoctocogene Roxaparvovec-rvox

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Valoctocogene roxaparvovec-rvox (Roctavian) **may be considered medically necessary** if **ALL** of the following criteria are met:

1. Adult individuals ≥ 18 years of age and assigned male at birth; AND
2. Individual has a confirmed diagnosis of severe hemophilia A (factor VIII levels ≤ 1 IU/dL); AND
3. Individual has been receiving prophylaxis with factor VIII concentrates for at least 1 year; AND
4. Absence of Factor VIII inhibitors; AND
5. Absence of detectable anti-AAV5 capsid antibodies; AND
6. Individual does NOT have any of the following:
    a. Evidence of a bleeding disorder not related to hemophilia A;
    b. Platelet count < 100 x 10^9/L;
    c. Creatinine ≥ 1.5 mg/dL
    d. Liver cirrhosis;
    e. Significant liver dysfunction (defined as alanine aminotransferase, aspartate aminotransferase, total bilirubin, or alkaline phosphatase >2 x ULN or international normalized ratio ≥1.4);
    f. Significant liver fibrosis;
    g. Chronic or active hepatitis B;
    h. Evidence of active infection or immunosuppressive disorder, including hepatitis C and HIV;
    i. Active malignancy (except non-melanoma skin cancer);
    j. History of hepatic malignancy;
    k. History of arterial or venous thromboembolic events;
    l. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.

Repeat treatment of valoctocogene roxaparvovec-rvox (Roctavian) **is considered experimental, investigational, and/or unproven**.

Valoctocogene roxaparvovec-rvox (Roctavian) **is considered experimental, investigational, and/or unproven** for all other indications.

Policy Guidelines

None

Description

Hemophilia A
Hemophilia A, also called factor VIII deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII (FVIII), a clotting protein. Although it is passed down from parents to children, about one-third of cases found have no previous family history. (1)

According to the U.S. Centers for Disease Control and Prevention (CDC), hemophilia occurs in approximately 1 in 5,617 live male births. There are between 30,000 – 33,000 males with hemophilia in the United States. More than half of people diagnosed with hemophilia A have the severe form. Hemophilia A is four times as common as hemophilia B. Hemophilia affects all races and ethnic groups. (1)

Treatment
Valoctocogene roxaparvovec-rvox (Roctavian™) is an adeno-associated virus (AAV) vector-based gene therapy product. Roctavian is replication-incompetent and consists of an AAV serotype 5 capsid containing a DNA sequence encoding the B-domain deleted SQ form of the human coagulation factor VIII (hFVIII-SQ). Roctavian is derived from naturally occurring adeno-associated virus and is produced using Sf9 insect cells and recombinant baculovirus technology. Valoctocogene roxaparvovec-rvox is designed to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of hFVIII-SQ. Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in the expression of hFVIII-SQ. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective hemostasis. (2)

Regulatory Status
Valoctocogene roxaparvovec-rvox (Roctavian™) (BioMarin Pharmaceutical Inc), an adeno-associated virus type 5 (AAV5) vector gene therapy product, received the U.S. Food and Drug Administration (FDA) approval on June 29, 2023. The FDA-approved indication is treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. Roctavian is a one-time treatment. Administration of Roctavian is contraindicated in (2):

- Individuals with active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B).
- Individuals with known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent), or cirrhosis).
- Individuals with known hypersensitivity to mannitol.

Rationale

The medical policy was developed in 2023 and is based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval as of July 30, 2024.

Valoctocogene roxaparvovec-rvox (Roctavian™)

The efficacy of Roctavian was evaluated in a prospective, phase 3, open-label, single-dose, single-arm, multinational study in 134 adult males (18 years of age and older) 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, were enrolled in the study. The study population was 72% White, 14% Asian, and 11% Black with a median age of 30 (range: 18 to 70) years. Twenty patients had a history of hepatitis B and 41 patients had a history of hepatitis C. All except 2 patients were human immunodeficiency virus (HIV)-negative. Only patients without detectable, pre-existing antibodies to adeno-associated virus serotype 5 (AAV5) capsid were eligible for therapy. Presence of pre-existing antibodies to AAV5 capsid was identified during screening using the Associated Regional and University Pathologists, Inc. (ARUP Laboratories) AAV5 DetectCDx™ total antibody assay, which is the FDA-approved test for selection of patients for Roctavian therapy. The exclusion criteria included the following:

1. Detectable pre-existing antibodies to the AAV5 capsid;
2. Any evidence of active infection or any immunosuppressive disorder, including HIV infection;
3. Significant liver dysfunction;
4. Prior liver biopsy showing significant fibrosis;
5. Evidence of any bleeding disorder not related to hemophilia A;
6. Platelet count of < 100 x 10^9/L;
7. Creatinine ≥ 1.5 mg/dL;
8. Liver cirrhosis of any etiology as assessed by liver ultrasound;
9. Chronic or active hepatitis B;
10. Active Hepatitis C;
11. Active malignancy, except non-melanoma skin cancer;
12. History of hepatic malignancy;
13. History of arterial or venous thromboembolic events;
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.

Of the 134 patients who received Roctavian in the clinical trial, 112 patients had baseline annualized bleeding rate (ABR) data prospectively collected during a period of at least six months on factor VIII prophylaxis prior to receiving Roctavian (rollover population). The remaining 22 patients had baseline ABR collected retrospectively (directly enrolled population). All patients were followed for at least 3 years. (2, 3)

The primary efficacy outcome was a non-inferiority (NI) 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 NI 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 the earliest. (2)

Table 1 summarizes the NI comparison between the mean ABR after Roctavian treatment and the mean baseline ABR while patients were on factor VIII prophylaxis in the rollover population (N = 112). The mean EEP ABR was 2.6 bleeds/year, compared to a mean baseline ABR of 5.4 bleeds/year. The mean difference in ABR was -2.8 (95% confidence interval: -4.3, -1.2) bleeds/year. The NI analysis met the pre-specified NI 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. (2)

Table 1. Summary of ABRs and Bleeding Events (Rollover Population, N = 112)

ABR and Bleeding Events	Baseline	Post-ROCTAVIAN Efficacy Evaluation Period
Median (range) follow-up duration in years	0.6 (0.5, 1.3)	3.0 (1.7, 3.7)
Follow-up duration in person-years	78.3	342.8
Mean (SD) ABR in bleeds/year	5.4 (6.9)	2.6 (6.2)[1]
Median (min, max) ABR in bleeds/year	3.3 (0, 34.6)	0.3 (0, 35.0)[1]
Observed spontaneous bleed count (proportion of total bleeds)	176 (42%)	179 (41%)
Observed joint bleed count (proportion of total bleeds)	240 (57%)	195 (45%)

Min: Minimum; Max: Maximum; SD: Standard Deviation; ABR: annualized bleeding rate.
[1] A total of 13 patients (12%) had used factor VIII replacement products or emicizumab during the efficacy evaluation period for prophylaxis, with a median start time at 2.3 (range: 0.1 to 3.3) years. An ABR of 35 was imputed for the periods when these patients were on prophylaxis.

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. (2)

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for

approval, valoctocogene roxaparvovec-rvox (Roctavian) may be considered medically necessary for individuals meeting the coverage criteria noted in this policy. Valoctocogene roxaparvovec-rvox (Roctavian) is considered experimental, investigational, and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1412

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. National Hemophilia Foundation. Hemophilia A. Available at: <https://www.bleeding.org> (accessed July 30, 2024).
2. The U.S. Food and Drug Administration (FDA). Roctavian-Highlights of prescribing information (June 2023). Available at: <https://www.fda.gov> (accessed July 30, 2024).
3. National Library of Medicine. Single-arm study to evaluate the efficacy and safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301) (BMN 270-301) (NCT03370913). Available at: <https://www.clinicaltrials.gov> (accessed July 30, 2024).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

09/15/2024	Document updated. The following changes were made to Coverage: Removed requirement for gamma glutamyl transferase and revised alkaline phosphatase criteria from >1.25 X ULN to >2 ULN. No new references added.
07/15/2024	Reviewed. No changes.
01/01/2024	New medical document. Valoctocogene roxaparvovec-rvox (Roctavian) may be considered medically necessary if ALL of the following criteria are met: 1. Adult individuals ≥ 18 years of age and assigned male at birth; AND 2. Individual has a confirmed diagnosis of severe hemophilia A (factor VIII levels ≤ 1 IU/dL); AND 3. Individual has been receiving prophylaxis with factor VIII concentrates for at least 1 year; AND 4. Absence of Factor VIII inhibitors; AND 5. Absence of detectable anti-AAV5 capsid antibodies; AND 6. Individual does NOT have any of the following: a. Evidence of a bleeding disorder not related to hemophilia A; b. Platelet count < 100 x 10^9/L; c. Creatinine ≥ 1.5 mg/dL; d. Liver cirrhosis; e. Significant liver dysfunction (defined as alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, or alkaline phosphatase >1.25 x ULN or international normalized ratio ≥1.4); f. Significant liver fibrosis; g. Chronic or active hepatitis B; h. Evidence of active infection or immunosuppressive disorder, including hepatitis C and HIV; i. Active malignancy (except non-melanoma skin cancer); j. History of hepatic malignancy; k. History of arterial or venous thromboembolic events; l. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation. Repeat treatment of valoctocogene roxaparvovec-rvox (Roctavian) is considered experimental, investigational, and/or unproven. Valoctocogene roxaparvovec-rvox (Roctavian) is considered experimental, investigational, and/or unproven for all other indications.