MEDICAL COVERAGE POLICY	
SERVICE:	**Valoctocogene roxaparvovec-rvox (Roctavian™)**
Policy Number:	**304**
Effective Date:	**10/01/2024**
Last Review:	**07/24/2024**
Next Review:	**07/24/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Valoctocogene roxaparvovec-rvox (Roctavian™)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Baylor Scott & White Health Plan (BSWHP) may consider valoctocogene roxaparvovec-rvox (Roctavian™) medically necessary for the treatment of severe hemophilia A in adult patients when ALL of the following criteria are met:

1. Member has a diagnosis of severe hemophilia A with FVIII activity ≤ 1 IU/dL; **AND**
2. The medication is prescribed by or in consultation with a hematologist; **AND**
3. Member age is ≥ 18 years; **AND**
4. Member has been receiving prophylactic FVIII, Antihemophilic Factor Recombinant FC-VWF-XTEN Fusion Protein-ehtl (Altuviiio) or emicizumab (Hemlibra) therapy for at least 1 year
5. The member does NOT have any of the following:
    a. FVIII inhibitors
    b. Detectable AAV5 antibodies
    c. HIV infection
    d. Substantial liver dysfunction (i.e. ALT, AST, GGT, total bilirubin, or Alk Phos >1.25 x ULN or INR ≥1.4), substantial liver fibrosis (grade 3 or 4 on Batts-Ludwig or METAVIR scoring system), or liver cirrhosis
    e. Previous treatment with valoctocogene
6. Valoctocogene will not be used in combination with emicizumab (Hemlibra)

BSWHP considers repeat administration of valoctocogene roxaparvovec-rvox experimental and investigational because the effectiveness of this strategy has not been established

Valoctocogene roxaparvovec-rvox for the treatment of all other indications is considered experimental, investigational and/or unproven.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:

Hemophilia is a genetic disorder that impairs the body's ability for normal blood clotting which can lead to spontaneous bleeding and hemorrhages, as well as bleeding after injuries or surgery, and in some cases, it can be fatal. This condition usually occurs in males as an X-linked recessive disease. The 2 most common types of hemophilia are hemophilia A (Factor VIII deficiency) and hemophilia B (Factor IX deficiency); either type can lead to spontaneous bleeding and prolonged bleeding following an injury or surgical procedure.

Hemophilia A is about 4 times as common as hemophilia B, and about one-half of those affected have the severe form. According to a recent study, it is now estimated that there are ~30,000 males with hemophilia in the United States, with 76.5% having hemophilia A and 23.5% having hemophilia B, although ~60% of both types still have severe disease.

There are varying severities of both hemophilia A and B depending on the level of factor produced by the patient. Patients with severe hemophilia frequently experience bleeding even in the absence of trauma; those with moderate hemophilia experience less bleeding, and those with mild hemophilia usually experience bleeding only after obvious trauma. The severity classification system is based on the patient's factor activity level.

Hemophilia Severity Classification	
Disease Severity	**Clotting Factor Level**
Severe hemophilia	<1 IU/dL or <1% of normal
Moderate hemophilia	1–5 IU/dL or 1%–5% of normal
Mild hemophilia	5–40 IU/dL or 5% to <40% of normal

Primary treatment centers on replacing clotting factors FVIII and FIX either through episodic (on-demand) treatment or continuous prophylaxis. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) recommends that prophylaxis be considered optimal therapy for individuals 1 year of age and older with severe hemophilia A or B. Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding), with the aim of keeping the trough FVIII or FIX level above 1% between doses. One of the most challenging aspects of hemophilia management occurs when a patient develops antibodies, called inhibitors, and is no longer able to use factor replacement to treat bleeding or to provide prophylaxis against bleeding. Inhibitors develop in approximately 25%–30% of people with hemophilia A and in 1%–6% of people with hemophilia B, and those with severe hemophilia are at greatest risk. Patients with FVIII inhibitors are treated with

Genentech's Hemlibra (emicizumab-kxwh) or a combination of blood products that bypass the inhibited clotting factors (i.e. bypassing agents) and high-dose FVIII.

Gene therapy is a new area of study with unknown duration of effect. Most hemophilia gene therapy products in development are recombinant adeno-associated viral vector (AAV) based followed by lentiviral vectors. The goal of the vector is to deliver the therapeutic transgene to hepatocytes following a single peripheral intravenous infusion. A potential challenge for using AAV vector delivery in children with hemophilia is that the vector could be lost from dividing cells during the substantial liver growth that occurs during childhood, although there is no direct evidence that this will happen.

Up to 25% of people with hemophilia may have detectable preexisting AAV5 capsid–neutralizing antibodies, and even at low titers, they will be enough to significantly impair therapeutically useful AAV vector delivery. Following large animal studies for more than 10 years after vector delivery, it was found that the antibodies produced by the immune reaction are likely to neutralize any readministered vector with cross-reactivity that will even negate the effect of switching vector serotypes. Thus, it appears that current AAV therapies may only be delivered once, and research is ongoing for strategies to overcome this obstacle.

While acute adverse events following AAV vector delivery are rare, liver toxicity occurs in ~60% of patients between 4 and 12 weeks post vector delivery, with increased serum alanine aminotransaminase levels, decreased factor levels due to the death of transduced hepatocytes, and sometimes evidence of AAV capsid-specific cytotoxic T cells

The U.S. Food and Drug Administration (FDA) approved BioMarin's valoctocogene roxaparvovec-rvox (Roctavian™) on June 29, 2023 as a one-time treatment of adults with severe hemophilia A. It is a gene therapy that uses the AAV5 capsid to deliver a functional copy of the F8 gene designed to enable the body to produce factor VIII (FVIII). In the Phase 3 GENEr8-1 study (NCT03370913), participants receiving valoctocogene demonstrated substantial treatment benefits across multiple measures at 1 year or more after treatment. GENEr8-1 is an open-label, single-group, multicenter trial with 134 men ≥ 18 years of age with severe congenital hemophilia A (FVIII activity level ≤1 IU/dL) negative for FVIII inhibitors who had been receiving prophylactic FVIII replacement therapy for at least 1 year before enrollment. The primary 52-week results showed that, among the 132 HIV-negative participants, the mean FVIII activity level at Weeks 49 through 52 had increased by 41.9 IU per deciliter (95% confidence interval [CI], 34.1–49.7; P <0.001; median change, 22.9 IU per deciliter; interquartile range, 10.9 to 61.3). Mean annualized FVIII concentrate use and mean treated bleeding rates after Week 4 decreased post infusion by 99% and 84%, respectively. 49 – 52 weeks after infusion, 90.3% had either no treated bleeds or fewer treated bleeds compared to FVIII prophylaxis. At 104 weeks, 132 of 134 participants had a difference in the mean number of bleeding events between baseline and the post-prophylaxis period of –4.1 (95% CI, –5.3 to –2.9) events per year (–84.5%; P<0.001). Noninferiority margin was established at 3.5 events per year. The annualized rate of factor VIII use decreased by 98.2% between baseline and the post factor VIII prophylaxis period. At the end of Year 3, 92% of patients remained off prophylaxis.

All 134 participants had at least one adverse event, most of which were grade 1 or 2. The most common adverse events included ALT increase (82.8%), headache (38.1%), nausea (37.3%), and AST increase (35.1%). 22 participant (16.4%) reported serious adverse events, and 5 participants (3.7%) reported serious adverse events that were determined by the investigators to be related to the study drug. All serious adverse events resolved, and no participants died, withdrew because of adverse events, or developed FVIII inhibitors. At Weeks 49 through 52, 7 of 134 participants (5.2%) had FVIII activity levels >150 IU/dL, and no participants reported thromboembolism. Valoctocogene clinical trials excluded patients with preexisting antibodies to the AAV5 capsid, HIV infection, and patients with substantial liver disease.

The long-term data from the ongoing Study 270-201 (NCT02576795), a Phase 1/2 dose-escalation study of 6-year and 5-year post-treatment follow-up demonstrated the sustained hemostatic efficacy of Roctavian. 6-year results in the 6 × 10^13 vg/kg dose cohort found that all participants remained off prophylactic FVIII treatment at the time of the data cutoff. The mean cumulative ABR remained <1 and substantially below baseline levels; the mean ABR in Year 6 was 0.7, with a mean cumulative ABR reduction of 95% and FVIII use reduction of 96% through 6 years, compared to baseline. 5-year results in the 4 × 10^13 vg/kg dose cohort found that all participants remained off prophylactic FVIII treatment at the time of the data cutoff. Six months prior to the data cutoff, one participant temporarily resumed prophylactic FVIII treatment for 1 month, after which he was bleed-free through the last follow-up. The mean ABR in Year 5 for the 4 × 10^13 vg/kg cohort was 0.7, with a mean cumulative ABR reduction of 91% and FVIII use reduction of 93% through 5 years, compared to baseline.

Although the expression of the transferred gene appears to diminish over time, BioMarin projects, based on existing data, that treatment efficacy of Roctavian will last at least 8 years.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	
HCPCS Codes:	J1412 - Injection, valoctocogene roxaparvovec-rvox, per ml, containing nominal 2 x 10^13 vector genomes
ICD10 codes:	
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	07/27/2023	New policy

Updated	07/24/2023	Updated HCPCS code, applied new format and layout

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. BioMarin Pharmaceutical Inc. BioMarin Announces Stable and Durable Annualized Bleed Control for ROCTAVIAN™ in Largest Phase 3 Gene Therapy Study in Adults with Severe Hemophilia A; 134-Participant Study Met All Primary and Secondary Efficacy Endpoints at 3-Year Analysis. PRNewswire.com, Jan 08, 2023, https://www.prnewswire.com/news-releases/biomarin-announces-stable-and-durable-annualized-bleed-control-for-roctavian-in-largest-phase-3-gene-therapy-study-in-adults-with-severe-hemophilia-a-134-participant-study-met-all-primary-and-secondary-efficacy-endpoints-at-3-ye-301716007.html
2. Centers for Disease Control and Prevention. What is hemophilia? Accessed July 24, 2023. https://www.cdc.gov/ncbddd/hemophilia/facts.html
3. George LA, et al. Long-term follow-up of the first in human intravascular delivery of AAV for gene transfer: AAV2-hFIX16 for severe hemophilia B. Mol Ther. 2020;28(9):2073-2082. doi:10.1016/j.ymthe.2020.06.001
4. Nathwani AC, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. N Engl J Med. 2011;365(25):2357-2365. doi:10.1056/NEJMoa1108046
5. National Hemophilia Foundation. Hemophilia A. Accessed July 24, 2023. https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a
6. National Hemophilia Foundation. MASAC Document 241 - Recommendation Concerning Prophylaxis. Published February 28, 2016. Accessed July 24, 2023. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-241-recommendation-concerning-prophylaxis
7. Ozelo MC, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med. 2022;386(11):1013-1025. doi:10.1056/NEJMoa2113708
8. Roctavian (valoctocogene roxaparvovec) [prescribing information]. Novato, CA: BioMarin Pharmaceuticals Inc; June 2023.
9. Soucie JM, et al. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. Haemophilia. 2020;26(3):487-493. doi:10.1111/hae.13998
10. Stanford S, et al. Adenovirus-associated antibodies in UK cohort of hemophilia patients: A seroprevalence study of the presence of adenovirus-associated virus vector-serotypes AAV5 and AAV8 neutralizing activity and antibodies in patients with hemophilia A. Res Pract Thromb Haemost. 2019;3(2):261-267. doi:10.1002/rth2.12177

***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

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RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.