BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 09/27/23**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 09/27/23**
	CURRENT EFFECTIVE DATE: 02/15/24
	LAST CRITERIA REVISION DATE: 02/15/24
NEXT ANNUAL REVIEW DATE: 4TH QTR 2024	**ARCHIVE DATE:**

GENE THERAPY FOR SEVERE HEMOPHILIA A:

- **ROCTAVIAN (valoctocogene roxaparvovec-rvox)**

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for therapy:** Roctavian (valoctocogene roxaparvovec-rvox) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a physician within a Hemophilia Treatment Center
2. Individual is 18 years of age or older
3. Individual has a confirmed diagnosis of severe hemophilia A (congenital factor VIII deficiency with residual factor VIII activity of less than 1 IU/dL) **OR** has manifestations of severe hemophilia A
4. Individual must be on prophylactic FVIII replacement therapy for at least 12 months prior to request and that prophylactic FVIII replacement is discontinued following administration of Roctavian
5. There are well-documented bleeding episodes and FVIII usage over the previous 12 months
6. Individual is being treated or has been exposed to FVIII concentrates or cryoprecipitate for minimum of 150 exposure days (ex., three FVIII infusions per week for 52 weeks equals 156 exposure days)
7. Individual continues to experience major bleeding episodes or has several severe bleeds per year despite treatment with prophylactic factor VIII replacement therapy (ex., major/severe bleeding that involves the central nervous system, airway, hip, deep muscle with neurovascular injury, joints, or abdomen; bleeding that cannot be controlled with local therapies, or bleeding necessitating transfusion or urgent care/emergency room visit, or hospitalization)
8. There is documentation of a Bethesda assay or Bethesda assay with Nijmegen modification of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months (ex., Bethesda titer is calculated using values of residual FVIII activity between 25% and 75%. Residual activity levels of 75%, 50%, and 25% correspond to inhibitor titers of 0.4, 1.0, and 2.0 BU/mL, respectively)
9. There are **NO** FDA label contraindications that include:
   - Active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B)
   - Known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or METAVIR score or equivalent grade of fibrosis if an alternative scale is used), or cirrhosis

- Known hypersensitivity to mannitol

10. Individual does **NOT** have **ANY** of the following:

    - Antibodies to adeno-associated virus serotype 5 (AAV5) detected by the FDA-approved test ARUP Laboratories AAV5 DetectCDx
    - History of factor VIII inhibitors (neutralizing antibodies to factor VIII)
    - Concurrent use of isotretinoin
    - Concurrent use of efavirenz
    - Hepatic impairment
    - Chronic or active hepatitis C
    - History of hepatic malignancy
    - Renal impairment
    - Active malignancy
    - History of arterial or venous thromboembolic event
    - Known inherited or acquired or thrombophilia including conditions associated with increased thromboembolic risk, such as atrial fibrillation
    - Prior treatment with any vector or gene transfer agent
    - Any bleeding disorder not related to hemophilia A
    - Platelet count of less than 100 x 10^9/L

11. There is documentation or attestation by provider of **ALL** of the following:

    - Patient received education relating to alcohol abstinence
    - Patient received education relating to the use of concomitant medications

12. Dosing to follow prescribing information using the recommended dose of Roctavian of 6×10^{13} vector genomes per kilogram (vg/kg) body weight, administered as a single intravenous infusion

13. The Attestation for Roctavian Treatment form (see below) has been signed by the physician (or designee)

Approval duration: **1 single intravenous dose (1 gene therapy per lifetime)**

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

Required Outcomes Measurements:

- Lab results **demonstrating** that beginning at least twenty-three (23) weeks after product administration, patient factor VIII levels were less than 5 IU/dL, as measured by the average of:
  - Two (2) consecutive CSA measurements. **OR**

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  - Two (2) consecutive OSA measurements, separated in time from each other by at least one (1) week).
- Provider submits **documentation** supporting the identification of two (2) or more spontaneous bleeds within a given twenty-six (26) week period, **OR** one (1) life threatening spontaneous bleed including the dates of the events.
- Physician **attestation** that, individual resumed continuous prophylaxis therapy, continuous therapy is medically necessary fifty-two (52) weeks per year.

➢ Roctavian (valoctocogene roxaparvovec-rvox) is considered ***experimental or investigational*** when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Attestations for Roctavian Treatment

Physician Name: _____

Individual Name: _____ DOB**:** _____

➢ The Physician is responsible for filling out this form.
➢ All elements must be initialed, and the form must be signed by the Physician (or designee).
➢ Incomplete forms will be returned to acquire missing information, initial, signature, or date.
➢ Return completed form to BCBSAZ.

Physician Agreement:
- Physician to initial by each element and date and sign to show willingness to participate.
- Documentation may include, but is not limited to, chart notes, laboratory test results, claims records, and/or other information.

Initials:

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_____ I verify that the patient will be closely followed and monitored for progression of disease

_____ I agree to submit clinical outcomes data and information

_____ I agree to submit lab results demonstrating that beginning at least twenty-three (23) weeks after product administration, individual's factor VIII levels were less than 5 IU/dL, as measured by the average of:
- Two (2) consecutive CSA measurements **OR**
- Two (2) consecutive OSA measurements, separated in time from each other by at least one (1) week)

_____ I agree to submit documentation supporting the identification of two (2) or more spontaneous bleeds within a given twenty-six (26) week period, **OR** one (1) life threatening spontaneous bleed including the dates of the events

_____ I confirm that, the individual resumed continuous prophylaxis therapy, continuous therapy is medically necessary fifty-two (52) weeks per year

Provider (or designee) Signature: _____

Date: _____

Description:

Roctavian (valoctocogene roxaparvovec-rvox) is an adeno-associated virus vector-based gene therapy indicated 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. It is designed to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (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.

Congenital factor VIII (FVIII) deficiency (hemophilia A) is the most common, inherited, X-linked recessive, congenital coagulation factor deficiency. Deficiency of FVIII results in impaired hemostasis and increased bleeding tendency. The severity of hemophilia A is characterized as either severe, moderate, or mild, and is based on residual FVIII activity of <1 IU/dL, 1 to <5 IU/dL, or 5 to <40 IU/dL, respectively.

The hallmark of the disease is the tendency to bleed spontaneously. Individuals with severe disease have spontaneous bleeds and bleeding after minor trauma out of proportion to the degree of injury, while those

with moderate or mild disease in general have few to no spontaneous bleeds and require a greater degree of trauma to demonstrate a bleed. The most common (70-80%) site of bleeding is the joint, followed by bleeding into the muscle (10-20%). Bleeds at other sites are rare; intracranial hemorrhage occurs in <5% of subjects. Recurrent and untreated bleeding leads to chronic arthropathy, muscular atrophy, and deformities.

Management goal of hemophilia is to prevent spontaneous bleeds by administering exogenous, plasma derived or recombinant FVIII products that will maintain FVIII activity levels to a value of >1% to 5% (i.e., in the range of subjects with the moderate form of the disease.) Although a major advance in the treatment of hemophilia A, it remains common for severe hemophilia A individuals to continue to have multiple bleeding events on prophylactic therapy.

Definitions:

Types of prophylaxis for patients with hemophilia A

Type of prophylactic treatment	Definition
Episodic (on demand) treatment	Replacement factor given at the time of bleeding
Continuous (regular) prophylaxis	Replacement factor given to prevent bleeding for at least 45 of 52 weeks (85%) of a year
• Primary prophylaxis	Continuous prophylaxis started before age three years and before the second large joint bleed
• Secondary prophylaxis	Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy
• Tertiary prophylaxis	Continuous prophylaxis started after the onset of arthropathy to prevent further damage
Intermittent (periodic) prophylaxis	Replacement factor given to prevent bleeding for short periods of time such as during and after surgery

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	02/15/24	Revisions to guideline
Pharmacy and Therapeutics Committee	09/27/23	Approved guideline by Ad Hoc
Clinical Pharmacist	08/22/23	Development

Coding:

HCPCS: J1412

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Resources:

Literature reviewed 09/27/23. We do not include marketing materials, poster boards and non-published literature in our review.

1. Hoots WK, Lewandowska M.Gene therapy and other investigational approaches for hemophilia. In: UpToDate, Shapiro AD, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2023. Topic last updated on June 30, 2023. Accessed August 23, 2023.

2. Hoots WK, Shapiro AD. Clinical manifestations and diagnosis of hemophilia. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2023. Topic last updated on January 05, 2022. Accessed August 23, 2023.

3. Hoots WK, Shapiro AD. Hemophilia A and B: Routine management including prophylaxis. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2023. Topic last updated on June 09, 2023. Accessed August 23, 2023.

4. Hoots WK, Shapiro AD. Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2023. Topic last updated on March 04, 2022. Accessed August 23, 2023.

5. Hoots WK, Shapiro AD. Treatment of bleeding and perioperative management in hemophilia A and B. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through July 2023. Topic last updated on April 22, 2022. Accessed August 23, 2023.

6. Mahlangu J, Kaczmarek R, von Drygalski,A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. *N Engl J Med* 2023;388:694-705. DOI: 10.1056/NEJMoa2211075. Accessed August 24, 2023.

7. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *N Engl J Med* 2022;386:1013-25. DOI: 10.1056/NEJMoa2113708. Accessed August 23, 2023

8. Roctavian (valoctocogene roxaparvovec-rvox) product information, revised by BioMarin Pharmaceutica Inc. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 22, 2023.

9. Tice JA, Walton S, Herce-Hagiwara B, et al Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value; Evidence Report. Institute for

Clinical and Economic Review, December 22, 2022. https://icer.org/assessment/hemophilia-a-and-b-2022/. Accessed August 23, 2023.

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Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html