Medical Policy

BlueCross BlueShield Kansas
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Title: Hemophilia A Gene Therapy Medical Drug Criteria Program Summary

Professional / Institutional
Original Effective Date: March 1, 2024
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Current Effective Date: November 7, 2024

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Roctavian™ (valoctocogene roxaparvovec-rvox) IV suspension	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		1

See package insert for FDA preshttps://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Hemophilia A	Hemophilia A also called Factor VIII (FVIII) 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 mothers to children, about 1/3 of cases found have no previous family history.(8) Treatment for hemophilia A is dependent on several factors and there is not a universal therapy that will work for all patients. Clinically the hallmark of bleeding in hemophilia is bleeding into the joints, muscles, and soft tissues. The severity and the risk of that bleeding can be correlated to the residual factor activity that can be measured in the blood. Patients with severe disease have less than 1% residual activity, and often have zero. These are the patients who are at risk for spontaneous as well as traumatic bleeding. Having over 5% residual amount makes bleeding into the joints very unusual (although not inconceivable), and most bleeding is triggered only by trauma. Residual activity of 1-5% appears for the most part to prevent spontaneous bleeding, but patients can still be at risk for joint bleeds with even relatively minor trauma.(9)
Prophylaxis	The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(11) • Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia • Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding • Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications • Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation). • The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future • Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies • Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities
Inhibitor Development	Approximately 1 in 5 people with hemophilia A will develop an antibody – called an inhibitor – to the clotting factor concentrate(s) used to treat or prevent their bleeding episodes. Developing an inhibitor is one of the most serious and costly medical complications of a bleeding disorder because it

	becomes more difficult to treat bleeds. Inhibitors most often appear in the first 50 exposure days of clotting factor concentrates.(9,10)
Gene Therapy	Adeno-associated virus (AAV)- mediated gene therapy is increasingly recognized for its potential to treat many monogenic diseases, including hemophilia A and B, by means of delivery of complementary DNA encoding functional Factor VIII or Factor IX proteins, respectively.(2) Numerous human Phase 1/2 clinical trials for hemophilia B and A have been conducted over the past decade. These trials have incorporated modifications of promoters, transgenes, and adeno-associated virus (AAV) vector serotypes, resulting in varying adverse events and levels of Factor IX or Factor VIII. More Phase 1/ 2 trials are in planning stages, including with different transgene delivery systems (e.g., lentiviral vectors). Further, four Phase 3 trials, 2 each in Hemophilia B and A are underway. While the initial results offer the prospect of a potential cure for hemophilia, many questions regarding efficacy and safety remain.(3) Most ongoing trials have shown transient hepatic enzyme elevations, signifying toxicity, in at least a subset of clinical trial participants. The mechanisms behind this toxicity are not fully understood, but include:(3) • An immune response to vector capsid • Possible direct cellular toxicity due to stress from catabolizing the AAV capsid • A cellular stress response due to high transgene protein synthesis burden and/or • Hepatotoxicity resulting from interaction of vector and co-administered potentially hepatotoxic medications, e.g., efavirenz. While the mechanisms are not all understood, these adverse events support the need to counsel patients receiving gene therapy to avoid potentially hepatotoxic therapies such as within HAART and support the need for more studies to determine the mechanisms of liver toxicity complicating gene therapy.(3) The Medical and Scientific Advisory Council (MASAC) of NHF continues to emphasize the careful consideration of advances in gene therapy to quantify and mitigate the risks to patients and others, including evaluation in informative animal models (e.g., primates). MASAC supports human clinical trials that proceed with appropriate risk/benefit analysis and risk reduction. MASAC encourages continued research efforts to pursue adequate gene expression to achieve an absence of bleeding events without concern for hepatic and other injury. MASAC strongly suggests the sponsors of gene therapy clinical trials address the relevant unknowns during the clinical trial process, including but not limited to:(3) • Opportunities to treat subjects with pre-existing capsid antibodies • Develop strategies to re-treat clinical trial participants • Address potential liver damage short term and long term, including biopsy of treated livers • Durability of response • Clotting factor activity discrepancies • Genomic integration events • Strategies to treat children and

	• Confounders unique to the hemophilia population, including HIV, hepatitis, and the drugs used for treatment of these disorders • Use of other hepatotoxic agents, such as alcohol and acetaminophen should be carefully evaluated, especially during early timepoints following administration of AAV Each patient should receive individualized discussions whether gene therapy is an option for them. Not all patients are candidates for gene therapy and not all patients who are candidates for gene therapy will want to undergo it. Some recommendations for who are candidates for gene therapy are as follows:(4) • Patients who have a need for a significant improvement of therapy • Patients who require better protection than they are receiving with existing therapies such as: o Very active patients o Patients with increased bleeding by severely damaged joints o Patients with increased bleeding by anticoagulation o Elderly patients: need for anticoagulation, risk for falls • Patients who have problems with continuing with existing therapy • Patients who need to become independent from regular treatment Many gene therapy trials exclude patients who have HIV or AIDS. Some practitioners believe that patients with HIV who are well controlled would benefit from gene therapy. The World Health Organization (WHO) states that anti-retroviral therapy (ART) should be started for all individuals with HIV regardless of WHO clinical stage or CD4 count. Routine viral load and CD4 count monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART. CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed (viral load undetectable).(5,6) Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (i.e., two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.(5,6)
Efficacy	The efficacy of Roctavian was evaluated in a prospective, phase 3 open-label, single-dose, single-arm, multinational study in adult males (18 years of age and older) with severe hemophilia A. Patients received a single intravenous dose and entered in a follow-up period of 5 years. Only patients without detectable, pre-existing antibodies to AAV5 capsid 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 test abnormalities, history of thrombosis or thrombophilia, serum creatine greater than or equal to 1.4 mg/dL, and active malignancy.(1) The primary efficacy outcome was a non-inferiority test of the difference in annualized bleeding rate (ABR) in the efficacy evaluation period (EEP) following Roctavian administration compared with ABR during the baseline

	period in the rollover population. The non-inferiority 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 the patient completed the study, had the last visit, or withdrew or was lost to follow-up from the study, whichever was the earliest.(1) 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.(1)
Safety	Roctavian carries following contraindications:(1) • Active infections, either acute or uncontrolled chronic • Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis • Known hypersensitivity to mannitol

REFERENCES

Number	Reference
1	Roctavian Prescribing Information. BioMarin Pharmaceutical Inc. June 2023.
2	Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med 2020; 382:29-40.
3	Medical and Scientific Advisory Committee. MASAC Document Regarding Risks of Gene Therapy Trials for Hemophilia. Document #254. December 2018.
4	Pipe Steven, VandenDriessche T, Pasi J, Miesbach W. Moving Beyond Factor: Shifting the Paradigm in Hemophilia Through Gene Therapy. Medscape Education Series. Presented through a collaboration between the National Hemophilia Foundation and Medscape. December 2019. Accessed at https://www.medscape.org/viewarticle/922905
5	World Health Organization (WHO) Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. 2016 update.
6	World Health Organization (WHO) Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. June 2016.
7	BioMarin. Valoctocogene roxaparvovec clinical data presented at the Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Melbourne, Austrailia; 6-10 July 2019. (pre-approval information).
8	National Hemophilia Foundation. Bleeding Disorders A-Z/ Types/ Hemophilia-A. Accessed at https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a
9	National Hemophilia Foundation. One Size Does Not Fit All: Individualized Therapy. Dr Steven Pipe. February 2017. Accessed at https://www.hemophilia.org/educational-programs/education/online-education/one-size-does-not-fit-all-individualized-therapy
10	CDC Centers for Disease Control and Prevention. Inhibitors and Hemophilia. Accessed at https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html

Number	Reference
11	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J1412	Roctavian	valoctocogene roxaparvovec-rvox iv susp	20000000000000 VG/ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Roctavian	valoctocogene roxaparvovec-rvox iv susp	20000000000000 VG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of hemophilia A (also known as Factor VIII deficiency, or classic hemophilia) **AND** 2. ONE of the following: A. The patient has a Factor VIII baseline residual level less than or equal to 1 IU/dL (lab test required) **OR** B. The patient has a Factor VIII baseline residual level greater than 1 IU/dL and less than or equal to 5 IU/dL AND the prescriber has determined that the patient has a bleed history that simulates severe hemophilia A (medical records including lab test and bleed history required) **AND** 3. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's sex is male **OR** B. The requested agent is medically appropriate for the patient's sex (medical records required) **AND** 4. The patient is 18 years of age or over **AND** 5. The patient does NOT have active inhibitors to Factor VIII **AND** 6. The patient has a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months (test results required) **AND** 7. The patient is NOT on any bypassing agents (i.e., Feiba, NovoSeven) **AND** 8. ONE of the following: (medical records required) A. The patient is on prophylactic therapy with a Factor VIII agent (e.g., Advate, Eloctate, Recombinate) AND has had a minimum of 150 exposure days **OR** B. The prescriber has determined that the patient requires improved protection than they are receiving from their current therapy (e.g., patients with increased bleeding due to severely damaged joints, patients with increased bleeding due to need for anticoagulation, elderly patients with risk for falls) **AND** 9. ONE of the following: A. The patient is NOT HIV positive (medical records including lab tests within the past 3 months required) **OR** B. The patient is HIV positive AND is well controlled (i.e. viral load within the past 12 months less than 1000 copies/mL) (lab results within the past 12 months required) **AND** 10. The patient does NOT have another immunosuppressive disorder **AND** 11. The patient's hepatitis B surface antigen is negative (medical records including lab tests within the past 3 months required) **AND** 12. ONE of the following: A. The patient's hepatitis C virus (HCV) antibody is negative (medical records including lab tests within the past 3 months required) **OR** B. The patient's HCV antibody is positive AND the patient's HCV RNA is negative (medical records including lab tests within the past 3 months required) **AND** 13. The patient does NOT have another active infection **AND** 14. The patient does NOT have significant liver dysfunction as defined by abnormal elevation of any of the following: (lab results within the past 3 months required) A. ALT (alanine transaminase) 3 times the upper limit of normal B. Bilirubin above 3 times the upper limit of normal C. Alkaline phosphatase above 3 times the upper limit of normal D. INR (international normalized ratio) greater than or equal to 1.4 **AND** 15. The patient does NOT have creatinine greater than or equal to 1.5 mg/dL (lab results within the past 3 months required) **AND** 16. The patient does NOT have evidence of any bleeding disorder not related to hemophilia A **AND** 17. The patient does not have anti-AAV antibodies (e.g., AAV-5) titers that exceed labeling administration instructions (test results within the past 3 months required) see Viral Vector Table **AND** **Viral vector Table**

Agent	Vector
Roctavian (valoctocogene roxaparvovec-rvox)	AAV-5

Module	Clinical Criteria for Approval
	18. The patient has NOT had previous gene therapy for hemophilia A (including requested agent) **Length of Approval:** 1 course per lifetime

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

REVISIONS	
Policy Posted 02-01-2024 Effective 03-01-2024	Policy added to the bcbsks.com web site. • Policy maintained by Prime Therapeutics LLC
Policy Posted 10-08-2024 Effective 11-07-2024	Policy reviewed by Prime Therapeutics with non-clinical edits
	Updated Coding Section ▪ Added HCPCS code J1412