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**Effective Date: 08/08/2024**

**Roctavian™ (valoctocogene roxaparvovec)**

**HCPCS: J1412**

**Policy:**

*Requests must be supported by submission of chart notes and patient specific documentation.*

- A. Coverage of the requested drug is provided when all the following are met:
  - a. FDA approved age
  - b. Diagnosis of severe hemophilia A with factor VIII level < 1% IU/dL
  - c. Must not have detectable pre-existing immunity to the adeno-associated virus serotype 5 (AAV5) capsid
  - d. Must not have a history of inhibitors to factor VIII or a positive factor VIII inhibitor screen defined as greater than or equal to 0.6 Bethesda units prior to administration of Roctavian
  - e. Must have been treated with or exposed to factor VIII concentrates or cryoprecipitate for a minimum of 150 exposure days
  - f. Must be treatment experienced with Hemlibra® for at least 6 months and experienced treatment failure defined as any of the following:
    - i. Spontaneous soft tissue bleeding event
    - ii. Micro-bleeding into a joint
    - iii. Ongoing joint pain of a known target joint
  - g. Must not have received prior treatment with any gene therapy for hemophilia A or are being considered for treatment with any other gene therapy for hemophilia A
  - h. Must be being treated at a federally recognized hemophilia treatment center site
  - i. The requesting physician attests to providing clinical outcome information within the Audaire Health™ provider portal as requested by BCBSM
  - j. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.
  
- B. Quantity Limitations, Authorization Period and Renewal Criteria
  - a. Quantity Limits: Align with FDA recommended dosing
  - b. Authorization Period: 3 months
  - c. Renewal Criteria: Not applicable as no further authorization will be provided

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.

\*\*\*Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

### Background Information:

- Roctavian is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A without antibodies to adeno-associated virus serotype 5 (AAV5).
- Hemophilia A is a rare genetic bleeding disorder in which affected individuals have insufficient levels of factor VIII. It is the second most common type of hemophilia and caused by mutations in the F8 gene. The F8 gene is located on the X chromosome and thus the disease is inherited as an X-linked recessive trait. About 30% of cases are the result of spontaneous genetic mutations. Overall incidence is estimated at 1 in 5,000 male births.
- The symptoms and severity of hemophilia A may vary greatly from one person to another. Hemophilia A can range from mild to moderate to severe.
  - Mild hemophilia patients have a factor activity of 5% to 40% and usually do not experience any major problems in everyday life. It often goes unnoticed until puberty or adulthood when bleeding after surgery or a deep cut lasts longer than normal. These patients do not typically need prophylactic therapy and only require on-demand factor for injuries or surgeries.
  - Moderate hemophilia patients have a factor activity of 1% to 5% and may have occasional episodes of spontaneous bleeding from deep tissues such as joints and muscles. These episodes are usually associated with some injury or inciting event. Individuals with moderate hemophilia A are at risk for prolonged bleeding following surgery or trauma. Affected individuals are usually diagnosed by 5 or 6 years of age. The frequency of spontaneous bleeding episodes in individuals with moderate hemophilia A is highly variable resulting in some patients needing consistent prophylactic factor VIII and others only needing on-demand factor VIII for medical procedures.
  - Severe hemophilia patients have a factor level of less than 1% and often have bleeding for no known reason, especially in the joints and muscles. From infancy, patients bruise easily and as they become more active, learn to walk, and put more strain on their joints and muscles, bleeding starts to occur. Without preventative treatment, a young child may experience 2 to 5 spontaneous bleeding episodes per month.
- Hemophilia A should be suspected in individuals presenting with a history of easy bruising, spontaneous bleeding, particularly into the joints, muscles, and soft tissues, or excessive bleeding following trauma or surgery. If hemophilia is suspected, the clinician should obtain the patient's bleeding history and family history of abnormal or unexplained bleeding experienced by any siblings or maternal male relatives to assess patterns of inheritance and assist with diagnosis. A definitive hemophilia A diagnosis is based on a factor assay to demonstrate a deficiency of factor VIII. Once an individual is diagnosed with hemophilia A, the specific mutation in the F8 gene responsible for causing hemophilia may be identified.
- The current standard of care for hemophilia A is the use of factor VIII replacement therapy. There are two types of factor products available to treat hemophilia which include plasma derived factor, entirely made of plasma from human donations and recombinant factor, which is made by genetically engineered technology, both with standard and extended half-life products. All factor products have demonstrated to have similar safety and efficacy in clinical studies treating or reducing bleeding episodes with the apparent difference in the frequency of administration: up to three times weekly injections for standard products and weekly or every two weeks for extended half-life products.

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To be enrolled in the GENE8-1 trial, patients needed to be stable on factor VIII therapy for 12 months prior to Roctavian administration.

- Hemlibra (emicizumab) is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII in hemophilia A patients to restore hemostasis. It can be used to treat patients without inhibitors who continue having spontaneous bleeds on prophylactic factor VIII therapy. Failure of Hemlibra is denoted by spontaneous soft tissue bleeds, micro-bleeding into a joint, or ongoing joint pain of a known target joint.
- It is estimated that up to 30% of individuals with severe hemophilia A develop inhibitors against factor VIII replacement therapy. Inhibitors most often develop during childhood, especially during the first 20 exposure days. Exposure days are counted as a day during which a patient receives factor. Controlling bleeds is a greater challenge in hemophilia patients with inhibitors than in those without. Inhibitors to factor VIII are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient's physical functioning, capacity for physical activities, and quality of life. The definition of a positive inhibitor is a Bethesda titer of greater than or equal to 0.6 BU for factor VIII. Patients positive for factor VIII inhibitors or with a prior history of factor VIII inhibitors were excluded from the GENE8-1 trial. In order to limit the risk of inhibitor development following Roctavian therapy, the GENE8-1 study also required patients had greater than 150 prior exposure days to factor IX therapy before receiving gene therapy.
- Roctavian uses an AAV5 vector to deliver a functional copy of the F8 gene to the patient's liver where functional factor VIII is produced. Patients with high AAV5 antibody titers may not respond to gene therapy due to the antibodies neutralizing Roctavian before the functional F8 gene can be properly incorporated into the patient's genome. The GENE8-1 study excluded patients from the trial based on antibody titers and is only indicated in those without AAV5 antibodies.
- Roctavian has not been studied and there is no data to support use in combination with other gene therapies indicated for use in hemophilia A.
- The Audaire Health platform is a provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the Audaire Health™ provider portal at the requested cadence.

## References:

1. Roctavian [prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.; June 2023.
2. Clinicaltrials.gov. Study to evaluate the efficacy and safety of valoctocogene roxaparvovec, with prophylactic steroids in hemophilia A (GENE8-3) (NCT04323098). Available at: <https://classic.clinicaltrials.gov/ct2/show/NCT04323098>. Accessed on June 30, 2023.
3. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. *NEJM*. 2022 March 17; 386: 1013 – 25.
4. National Organization for Rare Disorders. Hemophilia A. 2022 Aug 31. Available at: <https://rarediseases.org/rare-diseases/hemophilia-a/?filter=ovr-ds-resources>. Accessed on July 5, 2023.
5. World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2020 August 3. Available at: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14046>. Accessed on: July 5, 2023.

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Policy History												
#	Date	Change Description										
1.8	Effective Date: 08/08/2024	Annual review of criteria was performed, no changes were made										
1.7	Effective Date: 08/10/2023	New policy. This criteria replaces previously approved preliminary criteria										
1.6	Effective Date: 07/10/2023	UM medical management system update for MAPPO and BCNA <table border="1" data-bbox="483 422 1369 632"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.5	Effective Date: 07/06/2023	UM medical management system update for BCBS and BCN <table border="1" data-bbox="483 709 1369 919"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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1.4	Effective Date: 04/06/2023	Annual review of criteria was performed, no changes were made										
1.3	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made										
1.2	Effective Date: 04/08/2021	Annual review of criteria was performed, no changes were made										
1.1	Effective Date: 04/16/2020	Criteria Update										
1.0	Effective Date: 08/15/2019	Preliminary Drug Review <table border="1" data-bbox="483 1276 1369 1486"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>No</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	No	BCNA	No
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\* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.