Roctavian™ (Valoctocogene Roxaparvovec-Rvox)

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Commercial Policy
· Roctavian™ (Valoctocogene Roxaparvovec-Rvox)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Ohio	None
Texas	Refer to drug-specific criteria found within the Texas Medicaid Provider Procedures Manual

Coverage Rationale

Hemophilia A (i.e., Factor VIII Deficiency, Classical Hemophilia)

Roctavian is proven and medically necessary for the treatment of hemophilia A (factor VIII deficiency) when all of the following criteria are met:[1]

- Patient is 18 years of age or older; **and**
- **Both** of the following:
  - Diagnosis of severe hemophilia A; **and**
  - Documentation of endogenous factor VIII levels less than 1% of normal factor VIII (< 0.01 IU/mL, < 1 IU/dL); **and**
- **One** of the following:
  - Patient is currently receiving chronic prophylactic Hemlibra (emicizumab) therapy; **or**
  - **Both** of the following:
    - Patient currently uses factor VIII prophylaxis therapy; **and**
    - Patient has had a minimum of 150 exposure days to a factor VIII agent

    or

- Patient has been determined to be an appropriate candidate for Roctavian by the Hemophilia Treatment Center based on willingness to adhere to initial and long-term monitoring and management

and

- Patient does not have a history of inhibitors to factor VIII greater than or equal to 0.6 Bethesda units (BU); **and**
- Patient does not screen positive for active factor VIII inhibitors as defined as greater than or equal to 0.6 Bethesda units (BU) prior to administration of Roctavian; **and**
- Patient does not have pre-existing immunity to the AAV5 capsid as detected by the FDA-approved companion diagnostic test AAV5 DetectCDx™; **and**
- Patient has not gone through Immune Tolerance Induction (ITI); **and**
- Liver health assessments including enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] and hepatic ultrasound and elastography are performed to rule out radiological liver abnormalities and/or sustained liver enzyme elevations; **and**
- **One** of the following:
  - Patient is not HIV positive; **or**
  - Patient is HIV positive and is virally suppressed with anti-viral therapy (i.e., < 200 copies of HIV per mL)

  and
- The patient's hepatitis B surface antigen is negative; **and**
- **One** of the following:
  - Patient's hepatitis C virus (HCV) antibody is negative; **or**
  - Patient's HCV antibody is positive, and the patient's HCV RNA is negative

  and
- The patient is not currently using antiviral therapy for hepatitis B or C; **and**
- Patient has not previously received treatment with Roctavian or other gene therapy product for the treatment of hemophilia A in the patient's lifetime; **and**
- Roctavian is delivered by or in consultation with a Hemophilia Treatment Center (HTC); **and**
- Prescriber attests that the patient's ALT and factor VIII activity will be monitored weekly for at least 26 weeks following administration of Roctavian and regularly thereafter per the monitoring schedule recommended in the prescribing information; **and**
- Prescriber attests that counseling has been provided to the patient to abstain from consuming alcohol for at least one year following administration of Roctavian and regarding how much alcohol may be acceptable for the patient in the longer term; **and**
- Roctavian dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be issued for no more than one treatment per lifetime and for no longer than 45 days from approval

Additional information relevant to the review process but not impacting the determination of medical necessity:

- Prescriber attests that the patient, while under the care of the prescriber, will be assessed for treatment efficacy including, but not limited to evaluation of factor VIII expression, breakthrough bleeding episodes, factor VIII product utilization, inhibitor development*; **and**
- Prescriber acknowledges that UnitedHealthcare may request documentation, not more frequently than biannually, and not for a period to exceed 5 years of follow-up patient assessment(s) including, but not necessarily limited to, evaluation of factor VIII expression, breakthrough bleeding episodes, factor VIII product utilization, inhibitor development while the patient is under the care of the prescriber*

*For quality purposes only, this information will not be considered as part of the individual coverage decision.

Roctavian is not proven or medically necessary for:

- The treatment of hemophilia B
- The treatment of mild or moderate hemophilia A
- The repeat administration of Roctavian for the treatment of hemophilia A
- The treatment of hemophilia A after previously receiving another factor VIII gene therapy product
- The routine combination treatment with chronically administered prophylactic therapy for hemophilia A
- The treatment of hemophilia A in patients less than 18 years of age
- The treatment of hemophilia A in patients with elevated AAV5 antibodies

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1412	Injection, valoctocogene roxaparvovec-rvox, per ml, containing nominal 2 x 10^13 vector genomes

Diagnosis Code	Description
D66	Hereditary factor VIII deficiency

Background

Hemophilia A is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. It is estimated that 400 babies are born with hemophilia A each year.[2] Hemophilia A is caused by a mutation in the gene encoding coagulation factor VIII (FVIII) resulting in a deficiency in the activity of FVIII, an essential cofactor in the intrinsic coagulation cascade. The clinical phenotype of hemophilia A patients is largely governed by the level of residual FVIII expression. Severe hemophilia A is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe hemophilia A remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved.[3,4]

Roctavian (valoctocogene roxaparvovec-rvox) 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.

Clinical Evidence

Proven

Hemophilia A

A phase 1/2 dose-escalation study evaluated valoctocogene roxaparvovec in nine men with severe hemophilia A.[3,4] One patient was in the low-dose cohort [Cohort 1: 6 x 10^{12} vector genomes per kilogram of body weight (vg/kg)], one patient was in the intermediate-dose cohort (Cohort 2: 2 x 10^{13} vg/kg), and seven were in the high-dose cohort (Cohort 3: 6 x 10^{13} vg/kg). An additional fourth cohort of 6 patients was later added who received a dose of 4 x 10^{13} vg/kg. Eligible participants were adults with severe hemophilia A, with no history of factor VIII inhibitor development and without detectable immunity to the AAV5 capsid. Patients were considered to have severe hemophilia A if their factor VIII (FVIII) levels had ever declined to 1 IU/dL or less. Patients were required to have at least 150 days of previous exposure to factor VIII concentrate or cryoprecipitate. For participants using on-demand factor VIII therapy, rather than continuous prophylaxis, the criterion for inclusion was at least 12 bleeding episodes in the 12 months before study entry.

Patients were excluded from the study if they had detectable antibodies to AAV5, detectable HIV viral load, evidence of significant liver dysfunction as defined by abnormal elevation greater than 3 times the upper limit of normal for ALT (alanine transaminase), bilirubin, alkaline phosphatase, or an INR (international normalized ratio) greater than 1.4, or liver cirrhosis. Potential participants who had a liver biopsy in the past 3 years were excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4. Additional exclusion criteria included a platelet count of less than 100,000/dL, serum creatinine of greater than or equal to 1.5 mg/dL, positive hepatitis B surface antigen, detectable hepatitis C viral load, or evidence of any active infection or immunosuppressive disorder.

In the high-dose cohort (6 x 10^{13} vg/kg), the factor VIII activity level was more than 5 IU/dL between weeks 2 and 9 after gene transfer in all seven participants, and the level in six participants increased to a normal value (> 50 IU/dL) that was maintained at 1 year after receipt of the dose. In the high-dose cohort, the median annualized bleeding rate among participants who had previously received prophylactic therapy decreased from 16 events before the study to 1 event after gene transfer, and factor VIII use for participant-reported bleeding ceased in all the participants in this cohort by week 22. The median annualized use of factor VIII fell from 138 infusions per year before the study to 2 infusions per year after gene transfer (mean reduction in rate, from 137 to 5 infusions per year) and was 0 after week 2. The median consumption of factor VIII decreased from 5,286 to 65 IU/kg per year.

In the three year follow up to the phase 1/2 study for cohorts 1, 2, and 3, two participants (one who had received 6 × 10^{12} vg/kg and one who had received 2 × 10^{13} vg/kg) had factor VIII expression of less than 1 IU/dL.[5] Seven participants who had received 6 × 10^{13} vg/kg (cohort 3) had a median factor VIII expression of 20 IU/dL. The mean factor VIII expression measured by chromogenic assay at the ends of years 1, 2, and 3 were 64 IU/dL (median, 60 IU/dL), 36 IU/dL (median, 26 IU/dL), and 33 IU/dL (median, 20 IU/dL), respectively. The mean annualized rate of bleeding events decreased by 96%, from a mean (±SD) of 16.3 ±15.7 events per year (median, 16.5 events per year) at baseline to 0.7 ±1.6 events per year (median, 0.0 events per year) at the end of year 3. At the end of study year 3, a total of six participants (86%) were free from bleeding events. In the year before study entry, the mean annualized number of factor VIII infusions per participant was 136.7 ±22.4 (median, 138.5); at the end of year 3, the mean annualized use of exogenous factor VIII decreased by 96% to a mean of 5.5 ±9.4 infusions (median, 0.0 infusions).

In the four-year follow-up, the six patients with data available from cohort 3 had a median factor VIII expression of 16.4 IU/dL. The mean factor VIII expression measured by chromogenic assay at the ends of years 1, 2, 3, and 4 continued to decline and were 64 IU/dL (median, 60 IU/dL), 36 IU/dL (median, 26 IU/dL), 33 IU/dL (median, 20 IU/dL), and 24 IU/dL (median 16.4 IU/dL) respectively. The mean annualized rate of bleeding events decreased by 96%, from a mean of 16.3 events per year (median, 16.5 events per year) at baseline to 0.8 events per year (median, 0.0 events per year) at the end of year 4. In the fourth year the mean ABR was 1.3 with a median ABR of 0. At the end of study year 4, a total of six of the seven participants (86%) were free from bleeding events and no participants were requiring prophylactic therapy. In the year before study entry, the mean annualized number of factor VIII infusions per participant was 135.6 (median, 136.5); at the end of year 4, the mean annualized use of exogenous factor VIII decreased by 96% to a mean of 5.4 infusions.[12]

Two years after infusion, six participants in cohort 4 who had received 4 × 10^{13} vg per kilogram had a mean factor VIII activity level of 21.0 IU/dL (median, 23 IU/dL) at the end of year 1 and 15 IU/dL (median, 13 IU/dL) at the end of year 2. The annualized rate of bleeding events decreased by 92%, from a mean of 12.2 ±15.4 events per year (median, 8.0 events per year) in the year before study entry to a mean of 1.2 ±2.4 events per year (median, 0.0 events per year) at the end of year 2. In the year before study entry, the mean annualized number of factor VIII infusions per participant was 146.5 ±41.6 (median, 155.5). At end of year 2, the mean annual use of exogenous factor VIII decreased by 95%, to a mean of 6.8 ±15.6 infusions (median, 0.5 infusions) and the median use of factor VIII was reduced from 155.5 infusions to 0.5 infusions per year.

In the three-year follow-up of the six participants in cohort 4 who had received 4 × 10^{13} vg per kilogram had a median factor VIII activity level of 7.9 IU/dL. The mean factor VIII expression measured by chromogenic assay at the ends of years 1, 2, and 3 continued to decline and were 21 IU/dL (median, 23 IU/dL), 15 IU/dL (median, 13 IU/dL), and 9.9 IU/dL (median 7.9 IU/dL) respectively. The mean annualized rate of bleeding events decreased by 93%, from a mean of 12.2 events per year (median, 8.0 events per year) in the year before study entry to a mean of 0.9 events per year at the end of year 3. In the year before study entry, the mean annualized number of factor VIII infusions per participant was 142.8 (median, 155.8). At end of year 3, the mean annual use of exogenous factor VIII decreased by 96%, to a mean of 5.7 annual infusions over the 3 years. In year 3, the mean annual infusion rate was 8.4 (median 1.5). At the end of study year 3, four of the six participants (67%) remained free from bleeding events, with five of the six, free of target joint bleeds. No participants required prophylactic therapy.[12]

The efficacy of valoctocogene roxaparvovec 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 valoctocogene roxaparvovec 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 HIV-negative. Only patients without detectable, pre-existing antibodies to AAV5 capsid were eligible for therapy. Presence of pre-existing antibodies to AAV5 capsid

was identified during screening using the ARUP Laboratories AAV5 DetectCDx™ total antibody assay, which is the FDA-approved test for selection of patients for valoctocogene roxaparvovec-rvox 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 function test abnormalities, history of thrombosis or thrombophilia, serum creatinine ≥ 1.4 mg/dL, and active malignancy. Of the 134 patients who received valoctocogene roxaparvovec 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 valoctocogene roxaparvovec-rvox (rollover population). The remaining 22 patients had baseline ABR collected retrospectively (directly enrolled population). All patients were followed for at least 3 years. 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 valoctocogene roxaparvovec-rvox 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. 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 valoctocogene roxaparvovec. A majority of patients treated with valoctocogene roxaparvovec-rvox received immunosuppressive medications, including steroids, to control elevations in transaminases and to prevent loss of transgene expression. In the rollover population, a total of 5 patients (4%) did not respond and 17 patients (15%) lost response to valoctocogene roxaparvovec-rvox 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 valoctocogene roxaparvovec-rvox treatment over a median time of 3.6 (range: 1.2 to 4.3) years.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Roctavian is indicated for the 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 (AAV5) detected by an FDA-approved test.

References

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Policy History/Revision Information

Date	Summary of Changes
05/01/2024	**Application** ***Mississippi*** • Updated language to indicate this Medical Benefit Drug Policy applies to the state of **Mississippi** **Supporting Information** • Archived previous policy version CS2024D0094D

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.