PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Gene Therapy – Roctavian Prior Authorization Policy
- Roctavian® (valoctocogene roxaparvovec-rvox intravenous infusion – BioMarin)

REVIEW DATE: 09/11/2024

OVERVIEW

Roctavian, an adeno-associated virus vector-based gene therapy, 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 detected by an FDA-approved test.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-7] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (< 1 IU/dL), moderate (1 IU/dL to 5 IU/dL), and mild (> 5 IU/dL to < 40 IU/dL); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease. These patients usually require routine prophylaxis with Factor VIII replacement therapy products or Hemlibra® (emicizumab subcutaneous injection) to prevent bleeding.

Clinical Efficacy

The efficacy of Roctavian was evaluated in one open-label, single-group, multinational Phase III trial (GENEr8-1) involving 134 adult males (≥ 18 years of age) with severe hemophilia A (Factor VIII activity level ≤ 1 IU/dL).[1,8,9] Patients involved in the trial did not have Factor VIII inhibitors (or a history of such inhibitors) and were receiving regular prophylaxis with Factor VIII products. Use of prophylactic Factor VIII therapy was not permitted during the trial, but could be used up to 4 weeks post Roctavian administration to allow the agent to have an effect. Other notable exclusion criteria were active infection, chronic or active hepatitis B or C, immunosuppressive disorder (including HIV), Stage 3 or 4 liver fibrosis, cirrhosis, liver function test abnormalities, a history of thrombosis or thrombophilia, serum creatinine ≥ 1.4 mg/dL, and active malignancy. Patients had to be treated or exposed to Factor VIII concentrates previously for a minimum of 150 exposure days. Use of systemic immunosuppressive agents (not including corticosteroids), or live vaccines within 30 days before Roctavian infusion prevented participation. In the 132 patients who completed more than 51 weeks of follow-up (and were HIV-negative), the mean Factor VIII activity level at Weeks 49 through 52 had increased by 41.9 IU/dL (a non-hemophilic range). Among the 112 patients enrolled from a noninterventional study who had baseline annualized bleeding rate information prospectively collected for at least 6 months before receiving Roctavian (the rollover population), the mean annualized rates of Factor VIII concentrate use and treated bleeding after Week 4 had decreased after Roctavian administration by 98.6% and 83.8%, respectively ($P < 0.001$ for both comparisons).[1,8,9] At Year 3 post Roctavian dosing the mean annualized bleeding rate in the rollover population in the efficacy evaluation period was 2.6 bleeds/year compared to a mean baseline of 5.4 bleeds/year (while using Factor VIII therapies); mean Factor VIII activity levels were 21 IU/dL at this timepoint (mild hemophilic range).[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Roctavian. Because of the specialized skills required for evaluation and diagnosis of patients treated with Roctavian as well as the monitoring required for adverse events and long-term efficacy, approval requires Roctavian to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Roctavian, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Roctavian as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Roctavian is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophilia A.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, and S):
   - **A)** Patient is male*; AND
   - **B)** Patient is ≥ 18 years of age; AND
   - **C)** Patient has not received Roctavian in the past **[verification in claims history required]**; AND
     Note: If no claim for Roctavian is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Roctavian.
   - **D)** Patient has severe hemophilia A as evidence by a baseline (without Factor VIII replacement therapy) Factor VIII level of < 1 IU/dL **[documentation required]**; AND
   - **E)** Patient does not have detectable pre-existing antibodies to adeno-associated virus 5 (AAV5) by an FDA-approved test **[documentation required]**; AND
   - **F)** According to the prescribing physician, the patient has a history of use of Factor VIII therapy for at least 150 exposure days; AND
   - **G)** Patient meets ALL of the following (i, ii, and iii):
     - **i.** Factor VIII inhibitor titer testing has been performed within the past 30 days **[documentation required]**; AND
     - **ii.** Patient does not currently have an inhibitor to Factor VIII **[documentation required]**; AND
     - **iii.** Patient does not have a history of Factor VIII inhibitors **[documentation required]**; AND
   - **H)** Prophylactic therapy with Factor VIII will not be given after Roctavian administration once adequate Factor VIII levels have been achieved; AND
     Note: Use of episodic Factor VIII therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.
   - **I)** Patient does not have a known hypersensitivity to mannitol; AND
   - **J)** Patient does not have chronic or active hepatitis B **[documentation required]**; AND
   - **K)** Patient does not have active hepatitis C **[documentation required]**; AND

L) Patient is not human immunodeficiency virus positive **[documentation required]**; AND
M) Patient does not have evidence of significant hepatic fibrosis or cirrhosis; AND
N) Patient meets ONE of the following (i or ii):
- **i.** Patient has undergone liver function testing within the past 30 days and meets ALL of the following (a, b, c, d, e, and f):
  - **a)** Alanine aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **b)** Aspartate aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **c)** Total bilirubin levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **d)** Alkaline phosphatase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **e)** Gamma-glutamyl transferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **f)** The International Normalized Ratio is < 1.4 **[documentation required]**; OR
- **ii.** If the patient had one or more of the laboratory values listed in *Criteria a-f* above that was not at the value specified in *Criteria a-f* above, then a hepatologist has evaluated the patient and has determined that use of Roctavian is clinically appropriate **[documentation required]**; AND

O) Within the past 30 days, the platelet count was ≥ 100 x 10^9/L **[documentation required]**; AND
P) Within the past 30 days, the creatinine level was < 1.4 mg/dL **[documentation required]**; AND
Q) Medication is prescribed by a hemophilia specialist physician; AND
R) Current patient body weight has been obtained within the past 30 days **[documentation required]**; AND
S) If criteria A through R are met, approve one dose of Roctavian to provide for a one-time (per lifetime) single dose of 6 x 10^{13} vector genomes per kg by intravenous infusion **[verification required]**.
Note: Roctavian is supplied in a carton (NDC 68135-927-48) that contains one single dose vial (NDC 68135-927-01) with an extractable volume of not less than 8 mL, containing 16 x 10^{13} vector genomes.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Roctavian is not recommended in the following situations:

1. **Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the pivotal trial.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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10. Madan B, Ozelo MC, Paheja P, et al. Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A. *J Thromb Haemost*. 2024;22:1880-1893.