Molina Clinical Policy
Roctavian (valoctocogene roxaparvovec): Policy No. 433

Last Approval: 12/11/2024
Next Review Due By: August 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses Roctavian (valoctocogene roxaparvovec) for the treatment of severe hemophilia A.

Hemophilia A (congenital Factor VIII deficiency) is an X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII, which may be inherited or arise from spontaneous mutation (NORD 2022). Factor VIII levels have been used to assess the severity of hemophilia A. Although levels of factor VIII do not perfectly correlate with clinical severity in any individual, there is no other widely accepted classification system. Severe disease is defined by factor levels that are less than 1% of normal, according to factor level classifications (Refer to 'Supplemental Information' section for additional information on severity). Current standard of care is factor VIII replacement therapy, with moderate to severe hemophilia A patients receiving prophylactic infusions of factor VIII. Unfortunately, break through bleeding still occurs and frequent infusions diminish quality of life. Gene therapy for the treatment of hemophilia A aims to alter the clinical phenotype of hemophilia to a milder form or cure it by increasing endogenous coagulation factor levels via the transfer of a functional gene encoding the deficient coagulation factor. In the absence of longer-term data, however, the durability of gene therapy remains unknown.

Roctavian (valoctocogene roxaparvovec, or valrox; formerly BMN 270), the first approved gene therapy for hemophilia A, adds a functional copy of the coagulation factor VIII gene back to a person with hemophilia A via a viral vector. The viral vector is an adeno-associated virus, serotype 5 (AAV5). The expression of the functional factor VIII gene is driven by a liver-selective promoter. A one-time infusion of Roctavian results in production of an active factor VIII clotting factor. Roctavian is indicated for the treatment of severe hemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to AAV5. Patients undergoing gene therapy may still require on-demand factor therapy, which should be accessible in cases such as trauma, surgery, and spontaneous bleeding.

FDA approval of Roctavian was granted in June 2023 based on phase 3 clinical trial data from 132 participants over a two-year period. The primary endpoint, mean annualized bleeding rate, decreased by 77% from baseline during treatment with Roctavian. In addition, factor VIII activity increased by a mean of 22 IU per deciliter.

The long-term durability of the clinical benefit and safety of gene therapy for hemophilia remains unknown as factor levels have been observed to decline over time. The uncontrolled study design, small numbers of patients studied, and relatively short follow-up also factor into the considerable uncertainty regarding the long-term net benefits of Roctavian (ICER 2022). There are also uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma due to the integration of liver-targeting AAV vector DNA into the genome. While there is a theoretical risk of hepatocellular carcinoma development (ICER 2022) the true risk is expected to be low given that AAV vectors are not prone to integrate into the host genome. A longer follow-up is required to fully assess the benefits and potential risks of this one-time treatment.

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Roctavian (valoctocogene roxaparvovec) for the treatment of hemophilia A **may be considered medically necessary** when **ALL** the following criteria with are met with relevant documentation:

1. A diagnosis of hemophilia A in adult males (age 18 and older)
2. Severe hemophilia A defined by Factor VIII baseline residual level less than or equal to 1 IU/dL
3. Member has been on prophylactic FVIII replacement therapy for at least 12 months
4. Member has a history of Factor VIII therapy for at least 150 exposure days
5. Member has not already received Roctavian, and is not being considered for other gene therapy, or investigational cellular therapy for hemophilia
6. No presence or history of Factor VIII inhibitors (Factor VIII inhibitor titer test results required)
   NOTE: The definition of a positive inhibitor is a Bethesda titer of > 0.6 Bethesda units (BU) for FVIII (World Federation of Hemophilia Guidelines, 3rd edition).
7. No history of Factor IX inhibitors
8. Negative test for pre-existing antibodies to AAV5 per FDA approved companion diagnostic assay
9. No history of hepatic malignancy, cirrhosis, or advanced liver fibrosis
10. Member has had a liver evaluation within the last 30 days and the following lab values are < 3 times the upper limit of normal:
    a. Alanine aminotransferase and Aspartate aminotransferase
    b. Total bilirubin and alkaline phosphatase
11. Member meets **ONE** of the following for HIV testing:
    a. Member is HIV negative documented by lab test within the past 3 months
    b. HIV positive AND well-controlled on anti-retroviral therapy
12. Member does not have evidence of active Hepatitis B or C:
    a. Member does NOT have an active infection with hepatitis B or C virus documented by lab tests within the past 3 months as evidenced by **ALL** of the following:
       i. negative hepatitis B surface antigen
       ii. negative hepatitis C virus (HCV) antibody, OR HCV antibody is positive AND HCV RNA is negative
    b. For members with a history of Hepatitis B or C exposure: Member is NOT currently using antiviral therapy for hepatitis B or C
13. Platelet count ≥ 100 x 10^9/L
14. Creatinine < 1.5 mg/dl
15. No active immunosuppressive disorder
16. No history of arterial or venous thromboembolic events

17. No history of known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation

LIMITATIONS AND EXCLUSIONS

There are three contraindications listed in the manufacturer's labeling.
1. Active acute infections or uncontrolled chronic infections
2. Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis
3. Known hypersensitivity to mannitol

The following are considered **experimental, investigational, or unproven** based on insufficient evidence:
1. Any indications other than those listed above
2. Any criterion listed above not met by the member or submitted without the required supporting documentation.

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by a board-certified hematologist in coordination with a Hemophilia Treatment Center for administration.

DOSING CONSIDERATIONS: Recommended dose is 6×10^{13} vector genomes per kilogram (vg/kg) as a one-time IV infusion.

MONITORING PARAMETERS: Member should be monitored according to FDA-approved labeling and best practice.

QUANTITY LIMITATIONS: ONE (1) treatment course of Roctavian per lifetime. Additional infusions will not be authorized.

ADMINISTRATION: Roctavian is considered a provider-administered therapy in a Hemophilia Treatment Center by a physician(s) with experience in the treatment of patients with hemophilia.

CONTINUATION OF THERAPY: Not applicable as this is a one-time therapy. Reauthorization requests or requests for additional therapy beyond a single dose are considered experimental and will not be authorized.

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Repeat administration of is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Roctavian. The evidence is insufficient to determine the effects on net health outcomes.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The Biologics License Application (BLA) for Roctavian in severe hemophilia A patients is supported by results from the phase 3 GENEr8-1 trial (NCT03370913) and five years of assessments from a smaller, ongoing phase 1/2 BMN 270-201 (NCT02576795). In 2024 Symington et al., reported results at year 7 of trial participants (NCT02576795) receiving one dose of valoctocogene for severe hemophilia A. Those results continue to show reduced annualized bleeding rates and factor VIII infusion rates as compared to baseline for most participants. The pivotal GENEr8-1 phase 3 trial included 134 patients with a 1-year follow-up (Ozelo et al. 2022). The FDA requested additional data before allowing approval. Data from the continuation of that trial focused on annualized bleeding rates at 2 years. This data was published in NEJM in 2023 (Mahlangu et al., 2023). The phase 1/2 BMN 270-201 included only 7 patients but had follow-up through 6 years (Pasi et al., 2021). The GENEr8-1 trial assessed factor VIII activity as a

primary outcome while the Phase 1/2 trial assessed treatment-related adverse events (AEs).

GENEr8-1 trial (NCT03370913). The pivotal Phase 3 GENEr8-1 trial is an **ongoing,** single-arm, open-label multinational study to evaluate the efficacy and safety of valrox in 134 men with severe hemophilia A who were on standard prophylactic replacement therapy.

Intervention: All participants received a single infusion of Roctavian (6 X 10^{13} vg/kg of body weight) and then followed for at least 49 weeks.

Key inclusion criteria: All study participants had severe hemophilia A at baseline (defined as less than or equal to 1 IU/dL of Factor VIII activity), were at least 18 years of age, had been receiving prophylaxis with factor VIII concentrates for at least 1 year before enrollment, and were negative for factor VIII inhibitors.

Key exclusion criteria: Presence of anti-AAV5 capsid antibodies, HIV infection (added as a criterion after a protocol amendment), and substantial liver dysfunction, substantial liver fibrosis, or liver cirrhosis.

The primary end point was the change from baseline in factor VIII activity (measured with a chromogenic substrate assay) during weeks 49 through 52 after infusion.
Following gene therapy, the median FVIII activity level in these patients increased significantly, rising to 23.9 IU/deciliter after one year.

- After one year, 37.9% of participants had FVIII activity of 40 IU/deciliter or higher, which is considered non-hemophilia levels. FVIII activity levels in the remaining participants ranged from 5 to 40 IU/deciliter, indicating mild hemophilia in 50%, and less than 5 IU/deciliter in 12.1%. According to the available data, FVIII activity generally decreased after treatment.

Secondary end points included the change in annualized factor VIII concentrate use and bleeding rates. Safety was assessed as AEs and laboratory test results. Treatment effectiveness studies included 132 trial participants (two were excluded due to HIV infection).

- The mean annualized rates of factor VIII concentrate use and treated bleeding after week 4 had decreased by 98.6% and 83.8%, respectively, among the 112 participants enrolled in a prospective noninterventional study ($p < 0.001$ for both comparisons).

Safety: All participants experienced at least one AE, with 22 of 134 (16.4%) reporting serious AEs. All serious adverse events resolved. No participant deaths. Alanine aminotransferase levels were elevated in 115 of 134 participants (85.8%) and were treated with immune suppressants.

Limitations of the study include the small, single-arm design and lack of head-to-head comparison between Roctavian and emicizumab, which is gradually replacing factor VIII prophylaxis as standard therapy in hemophilia A.

Long-term durability of Roctavian was not assessable in the GENEr8-1 study, however, considerable reduction in factor VIII levels were noted over the study interval. ICER notes Roctavian is unlikely to be a long-term cure for hemophilia A (ICER 2022). Concerns also persist over the long-term effects on hepatic function and the possibility of oncogenesis. Additional long-term data is needed to establish the durability of Roctavian in reducing bleeding and long-term complications, particularly as compared to standard of care factor replacement therapy.

Long et al 2024, reported 2-year follow up data on development of immunogenicity to the factor VIII protein and AAV5 capsid. No participant developed a meaningful factor VIII inhibitor response. All participants developed durable anti-AAV5 antibodies, however that did not appear to result in loss of factor VIII activity.

Madan et al 2024, reported 3-year follow-up data from the GENEr8 study. Overall, hemostatic efficacy was not only maintained but remained better compared to those on standard prophylaxis over 3 years. At week 156 it was noted that 17 of 134 participants did resume prophylaxis.

GENEr8-1 is due to conclude in **November 2024.**

The manufacturer of Roctavian also completed the FDAs request for additional, longer-term data from trial NCT03370913 focusing on annualized bleeding rates. This data was published in the NEJM (Mahlungu et al. 2023) and results are summarized here. At week 104 (2 years), data from a total of 132 participants were reported with the primary endpoint being treated annualized bleeding rates. The mean annualized bleeding rate decreased by 77% from baseline during treatment with Roctavian. Factor VIII activity increased by a mean of 22 IU per deciliter. No new safety signals emerged, and no new serious adverse events occurred during the study interval.

Post-Marketing Study. A long-term extension study to follow all clinical trial participants for up to 15 years and a post-approval registry study to follow patients in a real-world setting is proposed by the manufacturer.

Ongoing trials

GENEr8-3 (NCT04323098), in a phase 3b, single arm, open-label study enrolled 20 males with severe hemophilia A, to evaluate the efficacy and safety of valrox at a dose of 6 x 10^{13} vg/kg with prophylactic corticosteroids in people with severe hemophilia A. Participants will be administered a single infusion of Roctavian with a regimen of anti-inflammatory corticosteroids, intended to dampen an immune response against the therapy's viral vector that may lower its effectiveness. The study's main goal is to assess the effect of treatment on FVIII activity, bleeding rates, and use of replacement therapy (Study BMN 270-303).

NCT03520712 is a Phase 1/2 Study of Roctavian dosed at 6 X 10^{13} vg/kg dose in patients with severe hemophilia A and pre-existing AAV5 antibodies to the AAV5 viral vector (Study 270-203). All participants will receive a single infusion of Roctavian, with the main goal of assessing safety after over five years of follow-up.

NCT04684940 is a Phase 1/2 Study of Roctavian dosed at 6 X 10^{13} vg/kg dose in patients with severe hemophilia A and or prior Factor VIII inhibitors, neutralizing antibodies to the FVIII protein, which can reduce the effectiveness of replacement therapies. The primary aim is to assess treatment's safety over five years (Study 270-205).

National and Specialty Organizations

World Federation of Hemophilia (WFH)

Guidelines for the Management of Hemophilia 2020, 3rd edition

The guidelines strongly advise that individuals with a severe phenotype of both hemophilia A and hemophilia B be on prophylaxis adequate to avoid all bleeding. Long-term prophylaxis is recommended as the standard of care, particularly in children, to prevent bleeding, hemarthrosis, and to improve quality of life. The prophylactic regimen should, whenever possible, be individualized for each patient based on bleeding phenotype, unique pharmacokinetics, and joint status. The guidelines do not specify a preference for recombinant over plasma-derived clotting factor concentrates and indicate that the selection between these product types should be determined based on availability, cost, and patient preferences.

For pediatric patients with severe hemophilia, WFH recommends initiating prophylaxis with clotting factor early (before age 3 and before the onset of joint disease). The dosing and interval for clotting factor prophylaxis (either standard or extended half-life) should be adequate to prevent spontaneous and breakthrough bleeding, as well as hemarthrosis. The WFH recommends escalation of prophylactic dose and orthopedic interventions in the event of a breakthrough bleed while on a prophylactic regimen.

The guidelines address gene therapy in general, noting that '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. This will require evaluation through long-term follow-up as part of clinical trials and registries.' The current 2020 guidelines include no specific recommendations for Roctavian.

A Gene Therapy Registry is being established to compile long-term data on the safety and efficacy of gene therapies in hemophilia to better understand the durability and variability of these therapies (Konkle et al. 2021).

Institute for Clinical and Economic Review (ICER)

ICER published the Final Evidence Report assessing the value of Valrox / Roctavian for hemophilia A (ICER 2022).

ICER concluded 'there is moderate certainty of a comparable, small, or substantial health benefit with high certainty

of at least a comparable net health benefit (C++) for valrox compared with factor VIII prophylaxis. Longer follow-up is required to fully assess the benefits and potential risks of this treatment.' The lack of direct evidence comparing valrox with emicizumab was noted, in addition to the indirect evidence suggesting that the short-term reduction in bleeding rates with valrox compared with factor prophylaxis are at least as great as that observed with emicizumab compared with factor prophylaxis. However, differences in the patient populations studied in the trials could be responsible for the observed benefits. Furthermore, there are clear initial adverse events with valrox (high risk of elevated liver enzymes requiring prolonged corticosteroid therapy). Because of the uncontrolled study design, small numbers of patients studied and short follow-up, there is still considerable uncertainty about the long-term net benefits of valrox compared with emicizumab. There are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valrox could be short-lived. The lack of direct data comparing the two therapies, the small number of treated patients, and the modest long-term follow-up leave considerable uncertainty about the net health benefits. ICER determined that 'there is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with emicizumab.

SUPPLEMENTAL INFORMATION

Hemophilia A disease severity is classified as mild, moderate, or severe based on the plasma concentration of Factor (normal activity level 50%-150%):

- **Mild** is defined as factor VIII activity > 5%-40% (> 0.05-0.4 units/mL), is usually diagnosed later in life, and is characterized by prolonged bleeding following major trauma or surgery.
- **Moderate** is defined as factor VIII activity ≥1%-5% (0.01-0.05 units/mL), is usually diagnosed between age 5 and 6 years, and is characterized by bleeding following minor trauma but may present with spontaneous bleeding.
- **Severe** is defined as factor VIII activity < 1% (< 0.01 units/mL), is usually diagnosed in the first 2 years of life and may present with spontaneous mild or life-threatening bleeding.

CODING & BILLING INFORMATION

CPT Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J1412	Injection, valoctocogene roxaparvovec-rvox, per ml, containing nominal 2 x 1013 vector genomes

AVAILABLE DOSAGE FORMS: ROCTAVIAN is a suspension for intravenous infusion. ROCTAVIAN has a nominal concentration of 2 × 1013 vg valoctocogene roxaparvovec-rvox per mL, each vial contains an extractable volume of not less than 8 mL (16 × 1013 vg).

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review.
08/14/2024	Updated medical summary with new data from newly published clinical trial.
08/09/2023	New policy. Policy was reviewed by practicing physician, Board-certified in Hematology July 14, 2023.

REFERENCES

1. BLA Approval. [June 30, 2023]. Accessed July 10, 2023. https://www.fda.gov/media/163466/download
2. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2014; 12(11):1935-1939. https://doi.org/10.1111/jth.12672.
3. Centers for Disease Control and Prevention (CDC). A New Study of Hemophilia Occurrence Finds Many More Cases in the United States. Updated August 8, 2022. https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-US.html
4. Centers for Disease Control and Prevention (CDC). Hemophilia. Page reviewed: August 1, 2022. https://www.cdc.gov/ncbddd/hemophilia/facts.html
5. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. Published 2021. https://www.clinicalkey.com/.
6. ClinicalTirals.gov. NCT03520712. Gene Therapy Study in Severe Hemophilia A Patients With Antibodies Against AAV5. Updated April 4, 2024. http://www.clinicaltrials.gov.
7. ClinicalTrials.gov NCT04684940. Safety, Tolerability, and Efficacy Study of Valoctocogene Roxaparvovec in Hemophilia A With Active or Prior Inhibitors. Updated July 5, 2024. https://www.clinicaltrials.gov.
8. ClinicalTrials.gov. NCT02576795. Gene Therapy Study in Severe Haemophilia A Patients (270-201). Updated December 15, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT02576795
9. ClinicalTrials.gov. NCT03370913. Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301) (BMN 270-301). Updated December 20, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03370913
10. ClinicalTrials.gov. NCT04323098. Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Hemophilia A. Updated April 4, 2024. http://www.clinicaltrials.gov.
11. DynaMed. Hemophilia A. EBSCO Information Services. Updated July 12, 2023. Accessed July 2024. http://www.dynamed.com.
12. FDA accepts BioMarin's Biologics License Application (BLA) for valoctocogene roxaparvovec AAV gene therapy for adults with severe hemophilia A. News release. BioMarin Pharmaceutical Inc. October 12, 2022. https://www.prnewswire.com/news-releases/fda-accepts-biomarins-biologics-license-application-bla-for-valoctocogene-roxaparvovec-aav-gene-therapy-for-adults-with-severe-hemophilia-a-301647823.html
13. Fong S, Yates B, Sihn CR, et al. Interindividual variability in transgene mRNA and protein production following adeno-associated virus gene therapy for hemophilia A. Nat Med. 2022;28(4):789-97. Epub 20220411. doi: 10.1038/s41591-022-01751-0. PubMed PMID: 35411075; PubMed Central PMCID: PMC9018415.
14. Hayes. Emerging Technology Report.: Valoctocogene Roxaparvovec (Roctavian; BioMarin Pharmaceutical) for Hemophilia A. Published July 2, 2023. Accessed July 2024. https://evidence.hayesinc.com/.
15. Hoots WK and Shapiro AD. Clinical manifestations and diagnosis of hemophilia. Updated June 26, 2024. https://www.uptodate.com/.
16. Institute for Clinical and Economic Review (ICER). Tice JA, Walton S, Herce-Hagiwara B, et al. Final Evidence Report: Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value. Published December 22, 2022. https://icer.org/.
17. Konkle BA, Coffin D, Naccache M, et al. The world federation of hemophilia gene therapy registry. Presented at: ISTH 2021 Congress; July 17-21, 2021. Abstract PB0661.
18. Long BR, Robinson TM, Day JRS, et al. Clinical immunogenicity outcomes from GENEr8-1, a phase 3 study of valoctocogene roxaparvovec, an AAV5-vectored gene therapy for hemophilia A. Mol Ther. 2024 Jul 3;32(7):2052-2063. doi: 10.1016/j.ymthe.2024.05.033. Epub 2024 May 24. PMID: 38796703.
19. Long BR, Veron P, Kuranda K, et al. Early Phase Clinical Immunogenicity of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A. Mol Ther. 2021;29(2):597-610. Epub 20201210. doi: 10.1016/j.ymthe.2020.12.008. PubMed PMID: 33309883; PubMed Central PMCID: PMC7854299.
20. Madan B, Ozelo MC, Raheja P, et al. Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A. J Thromb Haemost. 2024 Jul;22(7):1880-1893. doi: 10.1016/j.jtha.2024.04.001. Epub 2024 Apr 12. PMID: 38614387.
21. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. The New England journal of medicine. 2023;388(8):694-705. doi: 10.1056/NEJMoa2211075. PubMed PMID: 36812433.
22. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. The New England journal of medicine. 2022;386(11):1013-25. doi: 10.1056/NEJMoa2113708. PubMed PMID: 35294811.
23. Pasi KJ, Laffan M, Rangarajan S, et al. Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A. Haemophilia. 2021;27(6):947-956
24. Roctavian (valoctocogene roxaparvovec) [prescribing information]. Updated June 2023. Accessed July 2024. https://www.fda.gov/media/169937/download
25. Rosen S, Tiefenbacher S, Robinson M, et al. Activity of transgene-produced B-domain-deleted factor VIII in human plasma following AAV5 gene therapy. Blood. 2020;136(22):2524-34. doi: 10.1182/blood.2020005683. PubMed PMID: 32915950; PubMed Central PMCID: PMC7714098.
26. Soucie JM, Miller CH, Dupervil B, et al. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centers. Haemophilia. 2020 May;26(3):487-493. doi: 10.1111/hae.13998. Epub 2020 Apr 24. PMID: 32329553; PMCID: PMC8117262.

27. Srivastava A, Santagostino E, Dougall A, the WFH Guidelines for the Management of Hemophilia panelists and co-authors, et al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26(S6):1–158. doi: 10.1111/hae.14046. Epub 2020 Aug 3. Erratum in: Haemophilia. 2021 Jul;27(4):699. PMID: 32744769.
28. Symington E, Rangarajan S, Lester W, et al. Valoctocogene roxaparvovec gene therapy provides durable haemostatic control for up to 7 years for haemophilia A. Haemophilia. 2024 Jul 8. doi: 10.1111/hae.15071. Epub ahead of print. PMID: 38975624.