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Valoctocogene Roxaparvovec-rvox

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA)

when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Valoctocogene roxaparvovec-rvox (Roctavian) **may be considered medically necessary** for individuals if they meet criteria 1 through 10:

1. 18 years of age or older.
2. Assigned male at birth.
3. Severe or moderately severe hemophilia A as defined by residual factor VIII (FVIII) levels ≤1 IU/dL.
4. Currently receiving FVIII prophylaxis.
5. No history of FVIII inhibitors or a positive screen results of ≥0.6 Bethesda units (BU) using the Nijmegen-Bethesda assay.
6. No detectable pre-existing antibodies to the adeno-associated virus serotype 5 (AAV5) capsid.
7. A baseline liver health assessment including but not limited to alanine transaminase (ALT).
8. No history of receiving gene therapy.
9. Human immunodeficiency virus (HIV) negative or controlled HIV infection.
10. No active hepatitis B and/or hepatitis C infection.

Valoctocogene roxaparvovec-rvox (Roctavian) **is considered experimental, investigational, and/or unproven** for all other indications.

Repeat treatment with valoctocogene roxaparvovec-rvox (Roctavian) **is considered experimental, investigational, and/or unproven**.

Policy Guidelines

Recommended Dose
The minimum recommended dose is 6 X 10^{13} vector genomes (vg) per kg of body weight.

Dosing Limits
1 injection per lifetime.

Contraindications
Contraindications include:
- Active infections, either acute or uncontrolled chronic.
- Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis.
- Known hypersensitivity to mannitol.

Other Considerations
Valoctocogene roxaparvovec-rvox was not studied in individuals assigned female at birth.

It is recommended that prescribers perform regular alanine aminotransferase (ALT) testing at a certain frequency to monitor for elevations. Elevated liver enzymes, especially elevated ALT, may indicate immune-mediated hepatotoxicity and may be associated with a decline in factor VIII (FVIII) activity.

It is also recommended that prescribers monitor FVIII activity at the same frequency of ALT monitoring unless there are other clinical factors requiring additional monitoring (e.g., FVIII activity ≤5 IU/dL and evidence of bleeding). It may take several weeks after the valoctocogene roxaparvovec-rvox infusion before valoctocogene roxaparvovec-rvox-derived FVIII activity rises to a level sufficient for prevention of spontaneous bleeding episodes. Therefore, continued routine prophylaxis support with exogenous FVIII or other hemostatic products used in the management of hemophilia A may be needed during the first few weeks after infusion. After those initial weeks post-infusion, individuals should no longer require prophylaxis support with exogenous FVIII or other hemostatic products.

The use of the adeno-associated virus (AAV) vector DNA may carry the theoretical risk of hepatocellular carcinoma. It is recommended that prescribers monitor individual with risk factors for hepatocellular carcinoma with regular liver ultrasound and alpha-fetoprotein testing for 5 years after administration.

Description

Congenital Hemophilia

Most commonly, hemophilia is an inherited X-linked recessive congenital disorder that predominantly affects males caused by deficiency of coagulation factor VIII (FVIII; hemophilia A) and factor IX (FIX; hemophilia B). In Hemophilia A, variants in the *FVIII* gene lead to the associated impairment of the normal coagulation cascade. (1) In hemophilia B, variant in the *F9* gene results in deficiency or functional defectiveness of FIX. (2, 3)

Hemophilia affects more than 1.2 million individuals (mostly males) worldwide. (4) Hemophilia A is more common than hemophilia B. Typically, the reported incidence of hemophilia A is approximately 1 in 4000 to 1 in 5000 live male births while incidence of hemophilia B has been reported to occur in approximately 1 in 15,000 to 1 in 30,000 live male births. Approximately one-third to half have severe disease (FIX activity <1% of normal). (4, 5) The exact prevalence of hemophilia in the United States (U.S.) is not known but is estimated to be around 33,000 based on data during the period 2012 to 2018. (6) Approximately 77% of all hemophiliacs in the U.S. have hemophilia A, of which 60% may have severe disease. The estimated incidence of hemophilia A in the U.S. is 1:5000 live male births. This translates to approximately 400 infants born each year with hemophilia A. There is no clear effect of geography itself on incidence or prevalence. All races and ethnic groups are equally affected. (7-9) World Federation of Hemophilia (WFH) data from 1998 to 2006 indicate a global trend of increased prevalence of hemophilia A in approximately 80% of surveyed countries. (10) Potential contributing factors include increased survival, improved diagnostic capabilities, a broader use of national registries and migration from areas with limited access to healthcare to areas with better access.

The severity of hemophilia has generally been defined by factor levels. (11) Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted. (12) Disease severity using factor level classifications is summarized in Table 1. Individuals with more severe hemophilia are more likely to have spontaneous bleeding, severe bleeding, and an earlier age of first bleeding episode, which can begin as early as birth. Those with severe disease, are at risk for potentially life threatening bleeding episodes and debilitating long-term complications. (1) Individuals with severe hemophilia typically experience frequent, spontaneous bleeds (1 to 2 times per week) in their muscles or joints. (13) Repeated, spontaneous bleeding in the joints (hemarthrosis)

results in joint inflammation and damage to joint cartilage and synovium leading to hemophilic arthropathy. (14) According to 1 study, hemophilic arthropathy was observed in >90% of those with severe hemophilia before the age of 30 years. (15) Severe hemophilia is almost exclusively a disease of males, although females can be affected in some rare cases (e.g., compound heterozygosity; skewed lyonization; X chromosome loss). In contrast, mild hemophilia has been reported in up to one-quarter of female carriers who are heterozygotes. Most commonly, hemophilia is inherited. However, sporadic disease (without a positive family history, presumed due to a new variant) is also common. Studies have demonstrated that sporadic causes account for as much as 55% of cases of severe hemophilia A and 43% of cases of severe hemophilia B. (16) In moderate and mild hemophilia A and B, approximately 30% are sporadic cases.

Table 1. Hemophilia Severity, Factor Levels and Symptoms (13)

Severity of Hemophilia[a]	Clotting Factor Levels	Symptoms
Mild	5% to 40% of normal	• Might bleed for a long time after surgery, dental extraction, or a very bad injury • Rarely bleeds unless injured (rarely has spontaneous bleeding)
Moderate	1% to 5% of normal	• Might bleed for a long time after surgery, a bad injury, or dental work • Might bleed for no clear reason (occasional spontaneous bleeding)
Severe	Below 1% of normal	• Bleed often into the joints and sometimes the muscles • Can bleed for no obvious reason (spontaneous bleeding)

[a] Severity of hemophilia is measured in percentage of normal factor activity in the blood, or in number of international units (IU) per milliliter (mL) of whole blood. The normal range of clotting factor VIII or IX in the blood is 40% to 150%. People with factor activity levels of less than 40% are considered to have hemophilia. Some people's bleeding pattern does not match their baseline level. In these cases, the phenotypic severity (bleeding symptoms) is more important than the baseline level of factor in deciding upon treatment options.

Diagnosis

Hemophilia should be suspected in individuals who present with a history of easy bruising; "spontaneous" bleeding (i.e., bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues; excessive bleeding following trauma or surgery. Diagnosis is made by assessing the patient's personal and family

history of bleeding and is confirmed through screening tests, including a complete blood count test and a blood coagulation tests, typically activated partial thromboplastin clotting time (aPTT) and a prothrombin time (PT) test. (17) Both tests measure the length of time it takes for blood to clot and are important in identifying the potential cause of bleeding; the aPTT test assesses the clotting ability of factors VIII, IX, XI and XII while the PT assay tests for factors I, II, V, VII and X. (18, 6) In the event of an abnormal aPTT result, diagnosis of hemophilia A or B is established by the following criteria:

- Diagnosis of hemophilia A requires confirmation of a factor VIII activity level below 40% of normal (below 0.40 international units [IU]/mL), or, in some circumstances where the factor VIII activity level is ≥40 percent, a pathogenic variant in the *F8* gene. A normal von Willebrand factor antigen (VWF:Ag) should also be documented to eliminate of the possibility of some forms of von Willebrand disease.
- Diagnosis of hemophilia B requires confirmation of a FIX activity level below 40% of normal, or, in some circumstances where the FIX activity level is ≥40%, a pathogenic variant in the *F9* gene. Newborns have a lower normal range of FIX activity; the normal newborn range should be used as a reference when evaluating factor levels in newborns.

Genetic testing is recommended to identify the specific disease-causing gene mutation and evaluate the risk of inhibitor development. (17) Diagnosis is usually at a younger age among patients with the severe (≤2 years) or moderate (<5 to 6 years) form of the disorder compared with those with mild disease who are typically diagnosed later in life or in adulthood. (8)

Current Treatment

Factor replacement therapy is provided via 1 of 2 modalities: prophylaxis (regular replacement) or on demand (episodic). Prophylaxis is primary (before a bleeding event has occurred) or secondary (a bleeding event has occurred), and continuous or intermittent (e.g., for a few months at a time). Individuals with hemophilia, particularly those with severe hemophilia, can be affected by development of inhibitors (antibodies that develop in response to exogenous administration of exogenous factors). In a 13-year U.S. longitudinal study of individuals with hemophilia, 11% to 17% of those with severe hemophilia and 3% of individuals with mild hemophilia developed inhibitors during follow-up. (19) The median age of inhibitor development for those with severe hemophilia A was 3 years or less in developed countries, and was approximately 30 years in those with moderate-to-

mild hemophilia, often following intensive FVIII exposure with surgery.
(1) Development of inhibitors is also associated with increased mortality. A retrospective analysis of Centers for Disease Control and Prevention (CDC) surveillance data in individuals with severe hemophilia A reported that odds of death among the subgroup with inhibitors was 70% higher than among the subgroup without inhibitors ($p<.01$). (20) In a retrospective claims analysis conducted in the Netherlands, all-cause mortality rates among individuals with non-severe hemophilia A were 5 times higher in the subgroup with inhibitors when compared with the subgroup without inhibitors. (21) Several factor preparations are available for prophylaxis, some prepared from human plasma, some prepared using recombinant technology including some with modifications to extend the half-life of the therapy.

Regulatory Status
On June 29, 2023, valoctocogene roxaparvovec-rvox (Roctavian; BioMarin Pharmaceutical Inc.) was approved by the U.S. Food and Drug Administration (FDA) 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. (22)

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Congenital Hemophilia A

Clinical Context and Therapy Purpose

The purpose of gene therapy in adults who have congenital severe hemophilia A is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- A novel mechanism of action or approach that may allow successful treatment of many individuals for whom other available treatments are not available or have failed or have yielded sub-optimal response
- Reduced treatment complexity such as avoidance of repeated intravenous infusion or subcutaneous injections.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals who are adults with congenital severe hemophilia A.

Interventions

The therapy being considered is valoctocogene roxaparvovec-rvox, an AAV5 mediated gene therapy designed to deliver a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in the expression of hFVIII-SQ. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective hemostasis.

Comparators

Life-long prophylaxis with exogenous factor replacement therapy is currently being used to manage individuals with congenital severe hemophilia A.

Outcomes

The general outcomes of interest are disease-specific survival, change in disease status, health status measures, quality of life, resource utilization, treatment-related mortality and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Valoctocogene roxaparvovec-rvox

The clinical development program is summarized in Table 2 and consists of 2 interventional studies (301 and 201). Both are single-arm, open-label trials. Of these, study 201 is a phase I/II study and is not reviewed in detail. The key trial for valoctocogene roxaparvovec-rvox is the phase III trial (study 301) that includes 134 participants and is reviewed in detail.

Table 2. Clinical Development Program for Valoctocogene Roxaparvovec-rvox

Study	BMN 270-301	BMN 270-201
NCT Number	NCT03370913	NCT02576795
Phase	3	2
Study Population	Adult males with hemophilia A and residual FVIII levels ≤1 IU/dL	Adult males with hemophilia A and residual FVIII levels ≤1 IU/dL
Status	Ongoing (results published at 1 year follow-up [23] and 2 year follow-up [24])	Ongoing (results published at 1 year follow-up [25], 3 year follow-up [26] and 7 year follow-up [27])
Study Dates	2017-Ongoing	2015-Ongoing
Design	Open-Label, Single-Arm Study	Open-Label, Single-Arm Study
Sample Size	134	15
Follow-Up	52 weeks (efficacy analysis)	52 weeks (efficacy analysis)

FVIII: Factor VIII; IU: international units; NCT: national clinical trial.

Nonrandomized Studies

Study characteristic and baseline patient characteristics and results are summarized in Tables 3 and 4, respectively. The prospective, open-label, single-dose, single arm, multi-national study enrolled adult males 18 years and older with severe hemophilia A (endogenous factor VIII [FVIII] level ≤1 IU/dL) as evidenced by their medical history. Study design involved a prospective lead-in period of at least 6 months with the intent to receive standard of care routine factor prophylaxis along with bleeding events. Of the 134 participants who received valoctocogene roxaparvovec-rvox, 112 had baseline annualized bleeding rate (ABR) data prospectively collected during a period of at least 6 months on FVIII prophylaxis prior to receiving gene therapy (rollover population). The remaining 22 participants had baseline ABR collected retrospectively (directly enrolled population). All patients are intended to be followed for 5 years. The study is on-going. For the efficacy evaluation for the U.S. Food and Drug Administration (FDA) approval, all patients were followed for at least 3 years.

The primary efficacy outcome was a non-inferiority test of difference in ABR in the efficacy evaluation period. All bleeding episodes were counted. Participants were allowed to continue prophylaxis if needed. Results are summarized in Table 5. The mean ABR after treatment and pre-treatment while patients were on FVIII prophylaxis in the rollover population (N=112) was 2.6 bleeds/year versus 5.4 bleeds/year. The mean difference in ABR was -2.8 (95% confidence interval [CI], -4.3 to -1.2) bleeds/year. The non-inferiority analysis met the pre-specified margin of 3.5. According to the label, a total of 5 participants (4%) did not respond and 17 (15%) lost response to treatment over a median time of 2.3 years (range: 1.0 to 3.3). In the directly enrolled population with a longer follow-up, a total of 1 participant (5%) did not respond and 6 (27%) lost response to treatment over a median time of 3.6 years (range: 1.2 to 4.3).

The most common adverse reactions (incidence ≥5%) were nausea, fatigue, headache, infusion-related reactions, vomiting, and abdominal pain. Most common laboratory abnormalities (incidence ≥10%) were alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), FVIII activity levels, gamma-glutamyl transferase (GGT) and bilirubin above upper limit of normal (ULN). Transaminitis is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of AAV-vector based gene therapy. Most ALT elevations occurred within the first year following administration of gene therapy, especially within the first 26 weeks, were low-grade and resolved. The median time (range) to

the first ALT elevation (defined as ALT ≥1.5 x baseline or above ULN) was 7 weeks (0.4 to 159 weeks) and the median duration (range) was 4 weeks (0.1 to 135 weeks). Some ALT elevations were associated with a decline in factor VIII activity. As per the prescribing label, integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. As per the label, for individuals with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, and advanced age), regular (e.g., annual) liver ultrasound and alpha-fetoprotein testing should be performed following treatment.

Table 3. Summary of Key Nonrandomized Trial

Study	Study Type	Country	Participants	Treatment	Follow-Up
Study 301	Open-label, single-arm	Global	Inclusion • Males ≥18 years of age with severe hemophilia A and residual FVIII levels ≤1 IU/dL. • On prophylactic FVIII replacement therapy for at least 12 months prior to study entry. • No previous documented history of a detectable FVIII inhibitor. Exclusion • Detectable pre-existing antibodies to the AAV5 capsid. • Any evidence of active infection or any immunosuppressive	• Single intravenous dose of 6 X 10^{13} vg/kg body weight of valoctocogene roxaparvovec-rvox. • Of the 134 participants, 112 patients had ABR data prospectively collected for at least 6 months (rollover population); for remaining 22 participants baseline ABR data was collected retrospectively	5 years

			disorder, including HIV infection. • Active infection, chronic or active hepatitis B or C, immunosuppressive disorder including HIV. • 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. Primary endpoint • Non-inferiority test of the difference in ABR in the efficacy evaluation period[a] compared with baseline period in the rollover population. • Non-inferiority margin was 3.5 bleeds per year.	(directly enrolled population).	

AAV5: adeno-associated virus serotype 5; ABR: annualized bleeding rate; FVIII: factor VIII; HIV: human immunodeficiency syndrome; IU: international units.

[a] All bleeding episodes, regardless of treatment, were counted towards ABR. The efficacy evaluation period started from study day 33 (week 5) or the end of FVIII prophylaxis including a washout period after treatment with gene therapy, whichever was later, and ended when a participant completed the study, had the last visit, or withdrew or was lost to follow-up from the study, whichever was the earliest.

Table 4. Summary of Baseline Demographics and Disease Characteristics

Patient Characteristics in Study 301	**N=134**
Age, median (min to max), years	30 (18 to 70)
Race, n (%)	
White	72%
Asian	14%
Black	11%
Positive HIV status, n (%)	1%
Prior hepatitis B infection, n (%)	15%
Prior hepatitis C infection, n (%)	31%

HIV: human immunodeficiency virus.

Table 5. Summary of Results

Outcomes (Study 301)	**Pre-Study Period (n=112)**	**Post-Study Period (n=112)**	
Median (range) follow-up duration in years	0.6 (0.5 to 1.3)	3.0 (1.7 to 3.7)	
Follow-up duration in person-years	78.3	342.8	
Bleeding Related Outcomes (Primary)			
Mean (SD) ABR in bleeds/year	5.4 (6.9)	2.6 (6.2)[a]	
Median (min to max) ABR in bleeds/year	3.3 (0 to 34.6)	0.3 (0 to 35.0)[a]	
Observed spontaneous bleed count (proportion of total bleeds)	176 (42%)	179 (41%)	
Observed joint bleed count (proportion of total bleeds)	240 (57%)	195 (45%)	
Secondary Outcomes (Factor VIII Activity Thresholds)			
Chromogenic assay	**Year 1 (n=111), n (%)**	**Year 2 (n=99), n (%)**	**Year 3 (n=97), n (%)**
>150 IU/dL	6 (5%)	2 (2%)	2 (2%)
40 to ≤150 IU/dL	37 (33%)	14 (14%)	9 (9%)
15 to <40 IU/dL	37 (33%)	27 (28%)	23 (24%)
5 to <15 IU/dL	18 (16%)	33 (34%)	35 (36%)
3 to <5 IU/dL	3 (3%)	10 (10%)	8 (8%)

<3 IU/dL	10 (9%)	12 (12%)	19 (20%)
One-stage clotting assay, n (%)			
>150 IU/dL	12 (11%)	5 (5%)	4 (4%)
40 to ≤150 IU/dL	44 (40%)	25 (25%)	17 (18%)
15 to <40 IU/dL	37 (33%)	36 (36%)	36 (37%)
5 to <15 IU/dL	10 (9%)	20 (20%)	26 (27%)
1 to <5 IU/dL	6 (5%)	11 (11%)	12 (12%)
<1 IU/dL	2 (2%)	2 (2%)	2 (2%)

ABR: annualized bleeding rate; IU: international units; min: minimum; max: maximum; SD: standard deviation.

[a] A total of 13 participants (12%) had used FVIII replacement products or emicizumab during the efficacy evaluation period for prophylaxis, with a median start time at 2.3 (range: 0.1 to 3.3) years. An ABR of 35 was imputed for the periods when these patients were on prophylaxis.

The purpose of the study limitations tables (Tables 6 and 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of evidence supporting the position statement. The limited representation of African American, Asian, and Hispanic individuals makes it challenging to reach conclusions about the efficacy of valoctocogene roxaparvovec-rvox in these racial groups. The FDA reviewer noted a trend of lower FVIII activity levels in Black participants within the study population. Given the small sample size, the limited number of sites enrolling Black participants relative to the total population, the existence of potential confounding factors, and multiple *post hoc* analyses, this trend was insufficient to allow meaningful conclusions about the differences in response rates based on race or other factors influencing FVIII expression following valoctocogene roxaparvovec-rvox infusion. Despite differences in FVIII activity levels, ABR, and annualized FVIII usage was similar across races. Because of the uncontrolled study design, limited sample size and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec-rvox compared with factor prophylaxis. It is not yet clear that the initial increase in factor levels will be maintained for decades. In addition, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. The small sample size creates uncertainty around the estimates of adverse events. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect and safety.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Study 301	4. Enrolled populations do not reflect relevant diversity				1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 7. Study Design and Conduct Limitations

Study	Study 301
Allocation[a]	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias
Blinding[b]	1. Participants or study staff not blinded 2. Outcome assessors not blinded 3. Outcome assessed by treating physician 4. Outcomes not assessed centrally

Selective Reporting[c]	
Data Completeness[d]	
Power[e]	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on clinically important difference
Statistical[f]	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Valoctocogene roxaparvovec-rvox

The evidence for use of valoctocogene roxaparvovec-rvox for congenital hemophilia A consists of a single study. In the pivotal, open-label, phase III single-arm study, 134 study participants received a single intravenous infusion of valoctocogene roxaparvovec-rvox. Of the 134 participants, 112 were included in the efficacy analysis. The mean ABR after treatment with valoctocogene roxaparvovec-rvox was 2.6 bleeds/year compared with a mean ABR of 5.4 during the lead-in period yielding a mean difference of -2.8 (95% CI, -4.3 to -1.2) bleeds/year. This was within pre-specified non-inferiority margin of 3.5. The ABR represents an appropriate clinical benefit endpoint for individuals with hemophilia A, and the evidence of clinical benefit was demonstrated by reduction of bleeds during the post-treatment period. However, factor levels declined over time, and therefore benefits of valoctocogene roxaparvovec-rvox could be relatively short-lived. According to the label, a total of 5

participants (4%) did not respond and 17 (15%) lost response to treatment over a median time of 2.3 years (range: 1.0 to 3.3). In the directly enrolled population with a longer follow-up, a total of 1 participant (5%) did not respond and 6 (27%) lost response to treatment over a median time of 3.6 years (range: 1.2 to 4.3). Limitations include uncontrolled study design, limited sample size, and relatively short follow-up. There is considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec-rvox compared with FVIII prophylaxis. It is not yet clear that the initial increase in FVIII levels will be maintained for decades. In addition, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma as limited sample size is prone to uncertainty around the estimates for adverse events. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect and safety.

Summary of Evidence

For individuals who are adults with congenital hemophilia A who receive valoctocogene roxaparvovec-rvox, the evidence includes a single, prospective, single-arm study. Relevant outcomes are disease-specific survival, change in disease status, quality of life, resource utilization, treatment-related mortality and morbidity. In the pivotal, open-label, phase III single-arm study, 134 study participants received a single intravenous infusion of valoctocogene roxaparvovec-rvox. Of the 134 participants, 112 were included in the efficacy analysis. The mean annualized bleeding rate (ABR) after treatment with valoctocogene roxaparvovec-rvox was 2.6 bleeds/year compared with a mean ABR of 5.4 during the lead-in period yielding a mean difference of -2.8 (95% confidence interval [CI], -4.3 to 1.2) bleeds/year. This was within the pre-specified non-inferiority margin of 3.5. The ABR represents an appropriate clinical benefit endpoint for individuals with hemophilia A and the evidence of clinical benefit was demonstrated by reduction of bleeds during the post-treatment period. However, factor levels declined over time and therefore benefits of valoctocogene roxaparvovec-rvox could be relatively short-lived. According to the label, a total of 5 participants (4%) did not respond and 17 (15%) lost response to treatment over a median time of 2.3 years (range: 1.0 to 3.3). In the directly enrolled population with a longer follow-up, a total of 1 participant (5%) did not respond and 6 (27%) lost response to treatment over a median time of 3.6 years (range: 1.2 to 4.3). Limitations include uncontrolled study design, limited sample size, and relatively short follow-up. There is considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec-rvox compared with factor VIII prophylaxis. It is not yet clear that the initial increase in factor VIII levels

will be maintained for decades. In addition, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma as limited sample size is prone to uncertainty around the estimates for adverse events. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect and safety. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

Technology appraisal guidance on valoctocogene roxaparvovec for treating severe hemophilia A [ID3806] is in development and an expected publication date has not been released. (28)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 8.

Table 8. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT04323098	A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII, With Prophylactic Corticosteroids in Hemophilia A Patients	22	Jan 2027
NCT04684940	A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients With Active or Prior Inhibitors	10	Apr 2029
NCT05568719	GENEr8-JPN: A Phase 3 Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-	6	Mar 2029

	Mediated Gene Transfer of Human Factor VIII in Japanese Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions		

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1412

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. Jan 2013; 19(1):e1-e47. PMID 22776238
2. Goodeve AC. Hemophilia B: molecular pathogenesis and mutation analysis. J Thromb Haemost. Jul 2015; 13(7):1184-1195. PMID 25851415
3. Li T, Miller CH, Payne AB, et al. The CDC Hemophilia B mutation project mutation list: a new online resource. Mol Genet Genomic Med. Nov 2013; 1(4):238-245. PMID 24498619
4. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. Oct 15 2019; 171(8):540-546. PMID 31499529
5. Carcao MD. The diagnosis and management of congenital hemophilia. Semin Thromb Hemost. Oct 2012; 38(7):727-734. PMID 23011791
6. Centers for Disease Control and Prevention (CDC). Data & Statistics on Hemophilia. Available at <https://www.cdc.gov> (accessed July 5, 2025).

7. Mansouritorghabeh H. Clinical and laboratory approaches to hemophilia A. Iran J Med Sci. May 2015; 40(3):194-205. PMID 25999618
8. U.S. Food and Drug Administration. Guidance for Industry: Human Gene Therapy for Hemophilia. Available at <https://www.fda.gov> (accessed July 5, 2025).
9. National Organization for Rare Disorders. Hemophilia A. Available at <https://rarediseases.org> (accessed July 1, 2025).
10. Stonebraker JS, Bolton-Maggs PH, Soucie JM, et al. A study of variations in the reported haemophilia A prevalence around the world. Haemophilia. Jan 2010; 16(1):20-32. PMID 19845775
11. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. Nov 2014; 12(11):1935-1939. PMID 25059285
12. Pavlova A, Oldenburg J. Defining severity of hemophilia: more than factor levels. Semin Thromb Hemost. Oct 2013; 39(7):702-710. PMID 24026911
13. World Federation of Hemophilia (WHF). Hemophilia- How Severe is Hemophilia? Available at <https://www.wfh.org> (accessed July 5, 2025).
14. Melchiorre D, Manetti M, Matucci-Cerinic M. Pathophysiology of Hemophilic Arthropathy. J Clin Med. Jun 25 2017; 6(7):63. PMID 28672826
15. Jiang C, Zhao Y, Feng B, et al. Simultaneous bilateral total knee arthroplasty in patients with end-stage hemophilic arthropathy: a mean follow-up of 6 years. Sci Rep. Jan 25 2018; 8(1):1608. PMID 29371670
16. Kasper CK, Lin JC. Prevalence of sporadic and familial haemophilia. Haemophilia. Jan 2007; 13(1):90-92. PMID 17212731
17. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. Aug 2020; 26 Suppl 6:1-158. PMID 32744769
18. Kitchen S, McCraw A, Echenagucia M. Diagnosis of Hemophilia and Other Bleeding Disorders: A Laboratory Manual. 2nd Edition. 2010; Available at <https://www1.wfh.org> (accessed July 7, 2025).
19. Mazepa MA, Monahan PE, Baker JR, et al. Men with severe hemophilia in the United States: birth cohort analysis of a large national database. Blood. Jun 16 2016; 127(24):3073-3081. PMID 26983851
20. Walsh CE, Soucie JM, Miller CH. Impact of inhibitors on hemophilia A mortality in the United States. Am J Hematol. May 2015; 90(5):400-405. PMID 25616111
21. Eckhardt CL, Loomans JI, van Velzen AS, et al. Inhibitor development and mortality in non-severe hemophilia A. J Thromb Haemost. Jul 2015; 13(7):1217-1225. PMID 25912309

22. U.S. Food and Drug Administration (FDA). Roctavian-Highlights of prescribing information (June 2023). Available at: <https://www.fda.gov> (accessed October 26, 2025).
23. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. N Engl J Med. Mar 17 2022; 386(11):1013-1025. PMID 35294811
24. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. N Engl J Med. Feb 23 2023; 388(8):694-705. PMID 36812433
25. Rangarajan S, Walsh L, Lester W, et al. AAV5-Factor VIII Gene Transfer in Severe Hemophilia A. N Engl J Med. Dec 28 2017; 377(26):2519-2530. PMID 29224506
26. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med. Jan 02 2020; 382(1):29-40. PMID 31893514
27. 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. Sep 2024; 30(5):1138-1147. PMID 38975624
28. National Institute for Health and Care Excellence. Technology appraisal guidance TA989. Valoctocogene roxaparvovec for treating severe haemophilia A [ID3806]. Awaiting development [GID-TA10682]. Expected publication date: TBC. Available at <https://www.nice.org.uk> (accessed June 1, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2026	New medical document.