MASSACHUSETTS

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Medical Policy

Gene Therapies for Hemophilia A or B

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Policy Number: 168

BCBSA Reference Number: 8.01.65
NCD/LCD: N/A

Related Policies

Prior Authorization Request Form for Gene Therapies for Hemophilia B Hemgenix® (Etranacogene dezaparvovec), #169
Prior Authorization Request Form for Gene Therapies for Hemophilia A Roctavian® (Valoctocogene roxaparvovec-rvox), #166

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Entranacogene dezaparvovec-drlb (Hemgenix®)

Entranacogene dezaparvovec (Hemgenix) may be considered **MEDICALLY NECESSARY** and may be covered for individuals with Hemophilia B with congenital Factor IX deficiency when **ALL** the following criteria are met:

1. Individual is 18 years of age or older; **AND**
2. Individual has severe or moderately severe hemophilia B as defined by a plasma Factor IX (FIX) activity level ≤ 2%, as documented by written physician attestation AND historical records **OR** chart notes; **AND**
3. Must currently be on factor IX therapy with greater than 150 prior exposure days to treatment; **OR**
4. Individual meets one of the following:
    a. Current or historical life-threatening hemorrhage **OR**
    b. Repeated, serious spontaneous bleeding episodes; **AND**
5. Individual does not have a history of FIX inhibitors or a positive screen results of ≥ 0.6 Bethesda Units (BU) using the Nijmegen-Bethesda assay; **AND**
6. Individual has received a liver health assessment including enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] AND a hepatic ultrasound and elastography; **AND**
7. Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia B; **AND**

8. Individual does not have a history of receiving gene therapy or under consideration for treatment for another gene therapy for hemophilia B; **AND**
9. Individual is HIV negative or has a controlled HIV infection; **AND**
10. Individual does not have an active hepatitis B and/or hepatitis C infection.

Note: The safety and effectiveness of repeat administration of entranacogene dezaparvovec-drlb (Hemgenix) has not been evaluated. Therefore, coverage will be limited to once per lifetime.
The use of entranacogene dezaparvovec (Hemgenix) that does not meet the criteria as indicated in this policy is considered **EXPERIMENTAL/INVESTIGATIONAL** and therefore non-covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

entranacogene dezaparvovec-drlb is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment with entranacogene dezaparvovec-drlb is considered **INVESTIGATIONAL**.

entranacogene dezaparvovec-drlb is considered **INVESTIGATIONAL** for all other indications.

Valoctocogene roxaparvovec-rvox (Roctavian®)

Valoctocogene roxaparvovec-rvox (Roctavian) may be considered **MEDICALLY NECESSARY** and may be covered for individuals with congenital Hemophilia A when **ALL** the following criteria are met:

1. Individual is 18 years of age or older; **AND**
2. Assigned male at birth; **AND**
3. Diagnosis of severe or moderately severe hemophilia A as defined by residual Factor VIII (FVIII) levels ≤ 1 IU/dL; **AND**
4. Currently receiving FVIII prophylaxis; **AND**
5. No history of FVIII inhibitors or a positive screen results of ≥ 0.6 BU using the Nijmegen-Bethesda assay; **AND**
6. No detectable pre-existing antibodies to the adeno-associated virus serotype 5 (AAV5) capsid; **AND**
7. No history of receiving gene therapy or under consideration for treatment for another gene therapy for hemophilia A; **AND**
8. Medications is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia A; **AND**
9. A baseline liver health assessment including but not limited to ALT; **AND**
10. Educated regarding alcohol abstinence and concomitant use of certain medications (e.g., isotretinoin, efavirenz); **AND**
11. HIV negative; **AND**
12. No active hepatitis B and/or hepatitis C infection.

Valoctocogene roxaparvovec-rvox is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment with Valoctocogene roxaparvovec-rvox is considered **INVESTIGATIONAL**.

Valoctocogene roxaparvovec-rvox is considered **INVESTIGATIONAL** for all other indications.

Policy Guidelines

Entranacogene dezaparvovec-drlb

Recommended Dose: The minimum recommended dose is 2×10^{13} genome copies (gc) per kg of body weight.

Dosing Limits: 1 injection per lifetime

Other Considerations:
Where feasible, the individual should receive periodical monitoring for hepatotoxicity, hepatocellular carcinogenicity, FIX activity, and FIX inhibitors.

In cases of radiological liver abnormalities and/or sustained liver enzyme elevations, the prescriber is recommended to consider a consultation with a hepatologist to assess eligibility for etranacogene dezaparvovec-drlb.

Valoctocogene roxaparvovec-rvox

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

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.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required.**
Commercial PPO and Indemnity	Prior authorization is **required.**
Medicare HMO Blue℠	Prior authorization is **required.**
Medicare PPO Blue℠	Prior authorization is **required.**

Requesting Prior Authorization Using Authorization Manager
Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:

- Enter the facility's NPI or provider ID for where services are being performed.

- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources
- Refer to our Authorization Manager page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Gene Therapies using Authorization Manager for:
- Hemophilia B Hemgenix® (Etranacogene dezaparvovec) (169)
- Hemophilia A Roctavian® (Valoctocogene roxaparvovec-rvox), (#166)

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Procedure Codes

ICD-10 PCS Procedure Codes	Code Description
XW033F3	Introduction of Other New Technology Therapeutic Substance into Peripheral Vein, Percutaneous Approach, New Technology Group 3

Summary

Background – 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 reported incidences 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 percent of normal).[4,5,]The exact prevalence of hemophilia in the United States (US) 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 US have hemophilia A, of which 60% may have severe disease. The estimated incidence of hemophilia A in the US 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.[7,8,9,]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 estimated number of prevalent cases of hemophilia B in the US is between 6,300 and 7,600 as of 2018.[11,] Reported prevalence rate of hemophilia B was estimated at 3.7 per 100,000 male population while the incidence rate was estimated at 5.3 per 100,000 male births, or 1 case per 19,283 live male births. Worldwide, there are approximately 33,000 people living with hemophilia B as of 2020.[12,]

The severity of hemophilia has generally been defined by factor levels.[13,] Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted.[14,] 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.[15,] Repeated, spontaneous bleeding in the joints (hemarthrosis) results in joint inflammation and damage to joint cartilage and synovium leading to hemophilic arthropathy.[16,] According to 1 study, hemophilic arthropathy was observed in >90% of those with severe hemophilia before the age of 30 years.[17,]Severe hemophilia is almost exclusively a disease of males, although females can be affected in some rare cases (eg, 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.[18,] In moderate and mild hemophilia A and B, approximately 30% are sporadic cases.

Table 1. Hemophilia Severity, Factor Levels and Symptoms[15]

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	<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 millilitre (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.[19,] 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.[20,6,]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 factor IX activity level below 40% of normal, or, in some circumstances where the factor IX activity level is ≥40%, a pathogenic variant in the *F9* gene. Newborns have a lower normal range of factor IX 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.[19,]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 (eg, 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 US 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.[21,] 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).[22,] 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.[23,]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. An updated table is maintained by the of the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the United States (www.hemophilia.org).

Summary of Evidence

Etranacogene dezaparvovec-drlb (Hemgenix)

The evidence for use of etranacogene dezaparvovec-drlb for hemophilia B consists of a single study. In the pivotal, open-label, phase III single-arm HOPE-B study, 54 study participants received a single intravenous infusion of etranacogene dezaparvovec-drlb. Of the 54 participants, 53 were included in the efficacy analysis. The estimated mean annualized bleeding rate during months 7 to 18 after treatment with etranacogene dezaparvovec-drlb was 1.9 bleeds/year (95% CI: 1.0 to 3.4) compared with an estimated mean annualized bleeding rate of 4.1 (95% CI: 3.2 to 5.4) during the lead-in period. The annualized bleeding rate ratio (months 7 to 18 post-treatment / lead-in) was 0.46 (95% CI: 0.26 to 0.81) demonstrating non-inferiority of annualized bleeding rate during months 7 to 18 compared to the lead-in period. The ABR represents an appropriate clinical benefit endpoint for subjects with hemophilia B and the evidence of clinical benefit was demonstrated by reduction of bleeds in the efficacy evaluable period

post treatment. Limitations include uncontrolled study design, limited sample size and relatively short follow-up. There is considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec-drlb compared with factor IX prophylaxis. It is not yet clear that the initial increase in factor IX 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 clinical development program is summarized in Table 3 and consists of 3 interventional studies (AMT-060-01, AMT-061-01 and AMT-061-021). All 3 interventional studies are single-arm, open-label trials. Of these, the first two studies, AMT-060-01 and AMT-061-01 were phase 1/2 studies and are not reviewed in detail. The key trial for etranacogene dezaparvovec-drlb is the Phase 3 Hope-B trial (AMT-061-021) that includes 54 participants and is reviewed in detail.

Table 3. Clinical Development Program for Etranacogene dezaparvovec-drlb

Study	NCT No	Status	Study Dates	Objective	Sample Size	Follow-Up
CT-AMT-060-01	NCT02396342	Completed and published[21,]	2015 to 2021	To evaluate the long-term safety and efficacy of AMT-060 comprising an AAV5 vector carrying a codon-optimized wild-type *F9* transgene	10	5 years
CT-AMT-061-01	NCT03489291	Ongoing and interim results published[22,23,]	2018 to 2023	To confirm the safety and preliminary efficacy endpoints of AMT-061 (etranacogene dezaparvovec-drlb), with a modified *F9* transgene encoding the naturally occurring hyperactive mutation, FIX-Padua, in place of wild-type *F9*	3	5 years
CT-AMT-061-02 (HOPE-B)	NCT03569891	Ongoing	2018 to 2025	To evaluate the efficacy, and confirm the safety, of etranacogene dezaparvovec-drlb (as a progression of AMT-060).	54	5 years

allo-HSCT: allogenic hematopoietic stem cell transplant; CALD: cerebral adrenoleukodystrophy; eli-cel: elivaldogene autotemcel; FIX: factor IX.

Valoctocogene roxaparvovec-rvox (Roctavian)

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 annualized bleeding rate after treatment with valoctocogene roxaparvovec-rvox was 2.6 bleeds/year compared with an mean annualized bleeding rate 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 annualized bleeding rate 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.

Policy History

Date	Action
11/2023	New policy for valoctocogene roxaparvovec-rvox (Roctavian) added. Updated policy title to include gene therapies for hemophilia A. Added BCBSA reference policy number. Updated references. Clarified coding information. Effective 11/1/2023.
10/2023	Criteria # 3 for Hemgenix clarified to replace “AND” with “OR.”
9/2023	Hemgenix policy clarified to include prior authorization requests using Authorization Manager.
8/9/2023	Hemgenix policy revised. Updated criteria for medical necessity to include: 1) physician attestation and historical records or chart notes to establish severity of hemophilia B; 2) greater than 150 prior exposure days to treatment for current factor therapy criteria. Effective 8/9/2023.
5/2/2023	Updated Hemgenix criteria for medical necessity – Age, assigned sex at birth, disease severity, FIX therapy requirements, exclusion criteria, baseline test requirements
4/13/2023	Removed - Baseline anti-AAV5 antibodies > 1:678 in from criteria #5 list of exclusions. It is not an FDA requirement, and is not present in the HEMGENIX product label
04/03/2023	New medical policy for Hemgenix describing medically necessary and investigational indications. Policy created with literature review.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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