



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 B Beqvez® (Fidanacogene eleparvovec-dzkt), #[126](#)
- 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 BlueSM and Medicare PPO BlueSM Members**

Entranacogene dezaparvovec-drlb (Hemgenix®) and Fidanacogene eleparvovec-dzkt (Beqvez®)

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 $\leq 2\%$, 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: To support the data requirements for an outcomes-based agreement on this drug, the prescriber is encouraged to provide ongoing clinical information upon request by Plan or Plan's authorized representative (Evio Pharmacy Solutions).

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.

NOTE: To support the data requirements for an outcomes-based agreement on this drug, the prescriber is encouraged to provide ongoing clinical information upon request by Plan or Plan's authorized representative (Evio Pharmacy Solutions).

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.

Fidanacogene eleparvovec-dzkt

Recommended Dose: The minimum recommended dose is 5×10^{11} vector genomes (vg) per kg of body weight. The dosing is based on the individual's body mass index (BMI) in kg/m^2 . If the individual's BMI is $\leq 30 \text{ kg/m}^2$, actual body weight should be used. If the individual's BMI is $> 30 \text{ kg/m}^2$, dosing weight should be calculated using the following formula: $30 \text{ kg/m}^2 \times [\text{Height (m)}]^2$.

Dosing Limits: 1 injection per lifetime

Other Considerations:

Fidanacogene elaparvovec-dzkt was not studied in individual assigned female at birth.

It is recommended that alanine aminotransferase (ALT), aspartate aminotransferase (AST), and factor IX (FIX) activity levels are monitored once or twice weekly for at least 4 months post-infusion. If there is a transaminase elevation and/or decrease in FIX activity, institute corticosteroid treatment. It is also recommended that individuals limit alcohol consumption as alcohol may impact liver enzyme elevation and reduce factor IX activity over time.

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

Valoctocogene roxaparvovec-rvox

Recommended Dose: The minimum recommended dose is 6×10^{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 $\leq 5 \text{ IU/dL}$ 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 SM	Prior authorization is required .
Medicare PPO Blue SM	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](#))
- Hemophilia B Beqvez® (Fidanacogene eleparvovec-dzkt) ([#126](#))

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
C9399	Unclassified drugs or biologicals
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose
J1412	Injection, valoctocogene roxaparvovec-rvox, per mL, containing nominal 2×10^{13} vector genomes (Roctavian)
J1414	Injection, fidanacogene elaparvovec-dzkt, per therapeutic dose (BEQVEZ)
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 Symptoms¹⁵

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 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 $\geq 40\%$, 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	10	5 years

				AAV5 vector carrying a codon-optimized wild-type <i>F9</i> transgene		
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 <i>F9</i> transgene encoding the naturally occurring hyperactive mutation, FIX-Padua, in place of wild-type <i>F9</i>	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: allogeneic 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.

Fidanacogene elaparvovec-dzkt (Beqvez)

The prospective, open-label, single-dose, single arm, multi-national study enrolled adult males aged 19 to 75 years, with severe or moderately severe Hemophilia B. Study design involved a prospective lead-in period of at least 6 months with the intent to receive standard of care routine FIX prophylaxis. Study participants then received a single intravenous dose of fidanacogene elaparvovec-dzkt and entered a follow-up period of 6 years. Of the 45 patients, 41 completed at least 15 months of follow-up. The median follow-up of the 45 treated patients was 2.0 years (range: 0.4 to 3.2 years) from the time of infusion. The study is on-going.

The primary efficacy outcome was a non-inferiority test of ABR from week 12 (day 82) to data cutoff following treatment, compared with baseline ABR during the lead-in period. The first 81 days after infusion of gene therapy treatment was not included in the efficacy evaluation period to allow fidanacogene elaparvovec-dzkt to take effect. The ABR included treated and untreated bleeds, excluding procedural bleeds. The non-inferiority margin on the difference between ABR rates was 3.0 bleeds/year. Participants were allowed to continue prophylaxis during months 0 to 6. Results are summarized in Table 11. Six out of 45 study participants (13%) resumed routine FIX prophylaxis after treatment ranging from

0.4 years to 1.7 years after fidanacogene elaparvovec-dzkt infusion. An additional patient had intermittent exogenous FIX use and had a higher ABR post infusion (5.0 bleeds/year) compared to baseline (1.2 bleeds/year) with a FIX activity <5% starting at 0.4 years. To isolate the treatment effect from the confounding effect of prophylactic use of replacement products during the efficacy evaluation period, an ABR of 20 bleeds/year was imputed for this time period to approximate the hypothetical bleeding frequency in the absence of prophylactic use of replacement products. A supplemental analysis showed that the imputed ABR would need to be at least 40 bleeds/year in order for non-inferiority to not hold.³⁵ The model-derived mean ABR was 4.5 bleeds/year (95% CI, 1.9 to 7.2) during the baseline period and 2.5 bleeds/year (95% CI, 1.0 to 3.9) during post-treatment period, resulting in a difference of -2.1 bleeds/year (95% CI, -4.8 to 0.7). Since the upper bound of the 95% CI in the difference was less than 3.0 bleeds/year, it met the non-inferiority study success criterion.

In AAV vector-based gene therapies such as fidanacogene elaparvovec-dzkt, pre-existing anti-AAV neutralizing antibodies may impede transgene expression at desired therapeutic levels. A sustained increase in neutralizing anti-AAVRh74var antibodies was observed after administration of fidanacogene elaparvovec-dzkt in all patients who participated in clinical studies and had neutralizing antibody assessment. Transaminase elevations (defined as $\geq 1.5 \times$ baseline) occurred in 29 of 45 and 7 of 15 patients in study 1 and study 2 respectively. Twenty-eight (62%) patients in clinical study 1 received corticosteroids for transaminase elevation and/or decline in FIX activity. The mean time to corticosteroid initiation was 45 days. The mean duration of corticosteroid treatment was 113 days (range: 41 to 276 days). Transaminase elevation is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the AAV vector-based gene therapy. 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, monitor patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, advanced age) with regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing for 5 years following administration.³⁶

Study	Participants	Treatment
1002 (BeneGene-2) ³⁶ . - Global, Open-label, single-arm study 2019 - Ongoing	Inclusion - Adult males with severe or moderately severe (FIX activity ≤ 2 IU/dL) hemophilia - Completed at least 6 months of routine prophylaxis with FIX product in lead-in study 1004 (BeneGene-1) - Agree to suspend routine prophylaxis after gene therapy administration - At least 50 exposure days to FIX product (plasma-derived or recombinant) Exclusion - NAb titer $\geq 1:1$ for AAVRh74var capsid at screening - History of or current inhibitor to FIX (≥ 0.6 Bethesda units) - Active hepatitis B or C infection - HIV infection with CD4 cell count ≤ 200 mm³ or viral load > 20 copies/mL - Hypersensitivity to FIX product - ALT/AST/ALP > 2 times ULN, - Bilirubin > 1.5 times ULN - Unstable liver or biliary disease - Significant liver fibrosis (FibroScan score > 8 kPa units, FibroTest/FibroSure > 0.48, or AST-to-Platelet ratio > 1)	- All patients completed a prospective lead-in study of ≥ 6 months for baseline data collection while they received routine FIX prophylaxis in the usual care setting before entering clinical study 1. - Enrolled patients then received a single intravenous infusion of fidanacogene elaparvovec-dzkt at a dose of 5×10^{11} vg/kg of body weight and entered a follow-up period of 6 years. Follow Up: Median follow-up: 2.0 years (range: 0.4 to 3.2 years) from the time of infusion

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; EU: European Union; FIX: factor IX; NAb: neutralizing antibody; ULN: upper limit of normal; US: United States; UK: United Kingdom

Policy History

Date	Action
1/2025	Clarified coding information
10/2024	New policy for Beqvez describing medically necessary and investigational indications. Policy created with literature review.
3/2024	Clarified coding information and updated to add a note for Outcomes-based contracts.
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

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