Gene Therapies for Hemophilia B

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
New York	For **Hemgenix**: Refer to the state's Medicaid clinical policy
North Carolina	None
Ohio	None
Texas	Refer to drug-specific criteria found within the Texas Medicaid Provider Procedures Manual

Coverage Rationale

Hemophilia B (i.e., Congenital Factor IX Deficiency, Christmas Disease)

Beqvez is proven and medically necessary for the treatment of hemophilia B (congenital factor IX deficiency) when all of the following criteria are met:[1,3,10]

- Patient is 18 years of age or older; **and**
- **One** of the following:
  - **Both** of the following:
    - Diagnosis of severe hemophilia B; **and**
    - Documentation of endogenous factor IX levels less than 1% of normal factor IX (< 0.01 IU/mL)

    or
  - **All** of the following:
    - Diagnosis of moderately severe hemophilia B; **and**
    - Documentation of endogenous factor IX levels ≥ 1% ≤ 2% (greater than or equal to 0.01 IU/mL to less than or equal to 0.02 IU/mL); **and**
    - **One** of the following:
      - Patient has current or historical life-threatening hemorrhage; **or**
      - Patient has repeated, serious spontaneous bleeding episodes

and

- **One** of the following:
  - Patient currently uses factor IX prophylaxis therapy; **or**
  - Patient has been determined to be an appropriate candidate for Beqvez by the Hemophilia Treatment Center based on willingness to adhere to initial and long-term monitoring and management

  and
- Patient has had a minimum of 50 exposure days to a factor IX agent; **and**
- Patient does not have a history of inhibitors to factor IX greater than or equal to 0.6 Bethesda units (BU); **and**
- Patient does not screen positive for active factor IX inhibitors as defined as greater than or equal to 0.6 Bethesda units (BU) prior to administration of Beqvez; **and**
- Patient does not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test; **and**
- Patient has not gone through immune tolerance induction (ITI); **and**
- Liver health assessments including enzyme testing [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin], and hepatic ultrasound, and/or elastography are performed to rule out radiological liver abnormalities and/or sustained liver enzyme elevations; **and**
- **One** of the following:
  - Patient is not HIV positive; **or**
  - Patient is HIV positive and is virally suppressed with anti-viral therapy (i.e., < 200 copies of HIV per mL)

  and
- The patient's hepatitis B surface antigen is negative; **and**
- **One** of the following:
  - Patient's hepatitis C virus (HCV) antibody is negative; **or**
  - Patient's HCV antibody is positive, and the patient's HCV RNA is negative

  and
- The patient is not currently using antiviral therapy for hepatitis B or C; **and**
- Patient has not previously received treatment with Beqvez (fidanacogene elaparvovec-dzkt) or another gene therapy [e.g., Hemgenix (etranacogene dezaparvovec-drlb)] for the treatment of hemophilia B; **and**
- Beqvez is administered within a Hemophilia Treatment Center (HTC) that holds Federal designation as evidenced by being listed within the CDC's HTC directory;[11] **and**
- Prescriber attests that the patient's ALT and AST as well as factor IX activity will be monitored at least weekly for at least 4 months following administration of Beqvez and regularly thereafter per the monitoring schedule recommended in the prescribing information; **and**
- Prescriber attests that counseling has been provided to the patient around the risks of alcohol consumption following administration of Beqvez; **and**
- Beqvez dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be issued for no more than one treatment per lifetime and for no longer than 45 days from approval

Hemgenix is proven and medically necessary for the treatment of hemophilia B (congenital factor IX deficiency) when all of the following criteria are met:[1,3,10]

- Patient is 18 years of age or older; **and**
- **One** of the following:
  - **Both** of the following:
    - Diagnosis of severe hemophilia B; **and**
    - Documentation of endogenous factor IX levels less than 1% of normal Factor IX (< 0.01 IU/mL)

    or
  - **All** of the following:
    - Diagnosis of moderately severe hemophilia B; **and**
    - Documentation of endogenous factor IX levels ≥ 1% ≤ 2% (greater than or equal to 0.01 IU/mL to less than or equal to 0.02 IU/mL); **and**
    - **One** of the following:
      - Patient has current or historical life-threatening hemorrhage; **or**
      - Patient has repeated, serious spontaneous bleeding episodes

  and
- **One** of the following:
  - Patient currently uses factor IX prophylaxis therapy; **or**
  - Patient has been determined to be an appropriate candidate for Hemgenix by the Hemophilia Treatment Center based on willingness to adhere to initial and long-term monitoring and management

  and
- Patient has had a minimum of 50 exposure days to a factor IX agent; **and**

- Patient does not have a history of inhibitors to factor IX greater than or equal to 0.6 Bethesda units (BU); **and**
- Patient does not screen positive for active factor IX inhibitors as defined as greater than or equal to 0.6 Bethesda units (BU) prior to administration of Hemgenix; **and**
- Patient has not gone through immune tolerance induction (ITI); **and**
- Liver health assessments including enzyme testing [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin], and hepatic ultrasound, and/or elastography are performed to rule out radiological liver abnormalities and/or sustained liver enzyme elevations; **and**
- **All** of the following:
  - Documentation that the patient has been evaluated for the presence of preexisting neutralizing antibodies to the adenovirus vector (e.g., AAV-5) used to deliver the therapy; **and**
  - Patient has had pre-existing anti-AAV5 neutralizing antibodies measured through the laboratory developed, CLIA-validated AAV5 Neutralizing Antibody Test made available through CSL Behring; **and**
  - The patient does not have high anti-AAV antibody (e.g., AAV-5) titers that may be associated with a lack of response to treatment based on published clinical evidence

  and
- **One** of the following:
  - Patient is not HIV positive; **or**
  - Patient is HIV positive and is virally suppressed with anti-viral therapy (i.e., < 200 copies of HIV per mL)

  and
- The patient's hepatitis B surface antigen is negative; **and**
- **One** of the following:
  - Patient's hepatitis C virus (HCV) antibody is negative; **or**
  - Patient's HCV antibody is positive and the patient's HCV RNA is negative

  and
- The patient is not currently using antiviral therapy for hepatitis B or C; **and**
- Patient has not previously received treatment with Hemgenix (etranacogene dezaparvovec-drlb) or another gene therapy [e.g., Beqvez (fidanacogene elaparvovec-dzkt)] for the treatment of hemophilia B; **and**
- Hemgenix is administered within a Hemophilia Treatment Center (HTC) that holds Federal designation as evidenced by being listed within the CDC's HTC directory;[11] **and**
- Prescriber attests that the patient's ALT and AST as well as factor IX activity will be monitored weekly for at least 3 months following administration of Hemgenix and regularly thereafter per the monitoring schedule recommended in the prescribing information; **and**
- Prescriber attests that counseling has been provided to the patient around the risks of alcohol consumption following administration of Hemgenix; **and**
- Hemgenix dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be issued for no more than treatment per lifetime and for no longer than 45 days from approval

Additional information relevant to the review process for Beqvez and Hemgenix but not impacting the determination of medical necessity:
- Prescriber attests that the patient, while under the care of the prescriber, will be assessed for treatment efficacy including, but not limited to, evaluation of factor IX expression, breakthrough bleeding episodes, factor IX product utilization, inhibitor development;* **and**
- Prescriber acknowledges that UnitedHealthcare may request documentation, not more frequently than biannually, and not for a period to exceed 5 years of follow-up patient assessment(s) including, but not necessarily limited to, evaluation of factor IX expression, breakthrough bleeding episodes, factor IX product utilization, inhibitor development while the patient is under the care of the prescriber*

*For quality purposes only, this information will not be considered as part of the individual coverage decision.

Beqvez and Hemgenix are unproven and not medically necessary in the following:
- The treatment of hemophilia A
- The repeat administration of Hemgenix or Beqvez for the treatment of hemophilia B
- The treatment of hemophilia B after previously receiving another factor IX gene therapy product
- The routine combination treatment with chronically administered prophylactic therapy for hemophilia B
- The treatment of hemophilia B in patients less than 18 years of age

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
C9172	Injection, fidanacogene elaparvovec-dzkt, per therapeutic dose
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose
J3490	Unclassified drugs
J3590	Unclassified biologics

Diagnosis Code	Description
D67	Hereditary factor IX deficiency

Background

Hemophilia B is a genetic bleeding disorder resulting from missing or insufficient levels of blood clotting factor IX. Most individuals who have hemophilia B and experience symptoms are men. The prevalence of hemophilia B in the population is about one in 40,000; hemophilia B represents about 15% of patients with hemophilia.[2] Treatment typically involves replacing the missing or deficient clotting factor to improve the body's ability to stop bleeding and promote healing. Patients with severe hemophilia B typically require a routine treatment regimen of intravenous (IV) infusions of factor IX replacement products to maintain sufficient levels of clotting factor to prevent bleeding episodes.

The term "gene therapy" usually has been used to describe an ex vivo or in vivo therapy whereby RNA or DNA are introduced into target cells (ex vivo) or tissues (in vivo) by a delivery vector while "cellular therapy" is a broad term that encompasses both the infusion of a cellular product for the purpose of hematopoietic reconstitution and the infusion of a cellular product intended to have a direct immunologic impact.[9] There is a general consensus among the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the American Society of Gene and Cell Therapy (ASGCT), defining gene therapy as changes in gene expression achieved by replacing or correcting a disease-causing gene, inactivating a target gene, or inserting a new or modified gene, using a vector or delivery system of genetic sequence or gene, genetically modified microorganisms, viruses, or cells.[6,7,8] The rapid growth of cellular and gene therapies over the past few years has revealed the need for an accurate and uniform taxonomy. Work is ongoing across a number of industry stakeholders including clinicians, scientists, payers, and coders to standardize nomenclature regarding what constitutes a cellular therapy or a gene therapy.[9] In the United States, the FDA establishes the regulatory framework for clinical trials and approval of therapeutic agents such as gene and cellular therapy. Specifically, the FDA Center for Biologics Evaluation and Research regulates cellular therapy products and human gene therapy products as biologics, as well as some devices related to cellular and gene therapy.[7]

Beqvez is a one-time gene therapy product given as a single dose by IV infusion. Beqvez is based on recombinant DNA technology that consists of a recombinant viral capsid (AAVRh74var) derived from a naturally occurring AAV serotype (Rh74) vector containing the human coagulation factor IX (FIX) transgene modified to a high-specific factor IX activity variant known as FIX-R338L. Beqvez is designed to introduce in the transduced cells a functional copy of the factor IX gene encoding a high-activity FIX variant (FIX-R338L, hFIX Padua). The AAVRh74var capsid is able to transduce hepatocytes, the natural site of factor IX synthesis. Single intravenous infusion of Beqvez results in cell transduction and increase in circulating factor IX activity in patients with hemophilia B.

Hemgenix is a one-time gene therapy product given as a single dose by IV infusion. Hemgenix consists of a viral vector carrying a gene for clotting factor IX. Specifically, AAV5-hFIXco-Padua (AMT-061) is a recombinant adeno-associated viral vector of serotype 5 (AAV5) containing the Padua variant of a codon-optimized human FIX complementary deoxyribonucleic acid (cDNA) under the control of a liver-specific promoter.[3] The gene is expressed in the liver to produce factor IX protein, to increase blood levels of factor IX and thereby limit bleeding episodes.

Clinical Evidence

Proven

Hemophilia B

The efficacy of Beqvez was established in an ongoing, prospective, open-label, single-arm, study in 45 adult male patients with moderately severe to severe hemophilia B.[12] All patients completed a prospective lead-in study of at least six months for baseline data collection while they received routine factor IX prophylaxis in the usual care setting before entering the clinical study. Patients then received a single intravenous (IV) infusion of Beqvez. The main efficacy outcome was a non-inferiority (NI) test of annualized bleeding rate (ABR) during the efficacy evaluation period (EEP), week 12 to data cutoff following Beqvez treatment, compared with baseline ABR during the lead-in period. The model derived mean ABR was 4.5 bleeds/year (95% CI: 1.9, 7.2) during the baseline period and 2.5 bleeds/year (95% CI: 1.0, 3.9) during post-Beqvez EEP, resulting in a difference between the mean post-Beqvez EEP ABR and the baseline ABR of -2.1 bleeds/year (95% CI: -4.8, 0.7). The upper bound of the 95% CI in the difference was less than 3.0 bleeds/year, meeting the NI study success criterion. Six out of 45 patients (13%) resumed routine factor IX prophylaxis after Beqvez treatment, starting from 0.4 years to 1.7 years after Beqvez infusion.

The efficacy of Hemgenix was established in an open-label, single-arm study in 54 adult male patients aged 19 to 75 years, with severe or moderately severe hemophilia B. Patients prospectively completed a lead-in period of at least 6 months with the intent to receive standard of care routine factor IX prophylaxis. Patients then received a single IV dose of Hemgenix. The main efficacy outcome was a non-inferiority test of annualized bleeding rate (ABR) during months 7 to 18 after Hemgenix treatment compared with ABR during the lead-in period.

The estimated mean ABR during months 7 to 18 after Hemgenix treatment was 1.9 bleeds/year (95% CI: 1.0, 3.4), compared with an estimated mean ABR of 4.1 bleeds/year (95% CI: 3.2, 5.4) during the lead-in period. The ABR ratio (months 7 to 18 post-treatment/lead-in) was 0.46 (95% CI: 0.26, 0.81), demonstrating non-inferiority of ABR during months 7 to 18 compared to the lead-in period. Two patients were not able to stop routine prophylaxis after Hemgenix treatment. In one patient with a preexisting neutralizing anti-AAV5 antibody titer of 1:3212, no human factor IX expression was observed, and restart of the exogenous factor IX prophylaxis was needed for bleeding events. In a second patient, an infusion-related hypersensitivity reaction was observed after initiation of administration of Hemgenix and only 10% of the Hemgenix dose was administered. During months 7 to 18, an additional patient received prophylaxis from days 396 to 534. Warnings and precautions for Hemgenix include infusion reactions, hepatotoxicity, immune mediated neutralization of the AAV5 vector capsid, hepatocellular carcinogenicity, and monitoring laboratory tests. The most common adverse reactions (≥ 5%) with Hemgenix use were elevated alanine aminotransferase, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, malaise, and elevated aspartate aminotransferase.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Beqvez (fidanacogene elaparvovec-dzkt) is FDA-labeled for treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who currently use factor IX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, and do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

Hemgenix (etranacogene dezaparvovec-drlb) is FDA-labeled for treatment of adults with hemophilia B (congenital Factor IX deficiency) who currently use factor IX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

References

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Policy History/Revision Information

Date	Summary of Changes
10/01/2024	**Applicable Codes** • Updated list of applicable HCPCS codes to reflect quarterly edits; replaced C9399 with C9172 **Supporting Information** • Archived previous policy version CS2024D00120G

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.