BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 02/16/23**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 02/15/24**
	CURRENT EFFECTIVE DATE: 08/15/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 1ST QTR 2025	**ARCHIVE DATE:**

GENE THERAPY FOR HEMOPHILIA B

- **BEQVEZ™ (fidanacogene elaparvovec-dzkt)**
- **HEMGENIX® (etranacogene dezaparvovec-drlb)**

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

BEQVEZ (fidanacogene elaparvovec-dzkt)

- **Criteria for initial therapy:** Beqvez (fidanacogene elaparvovec-dzkt) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a Hematologist at or in consultation with a Hemophilia Treatment Center (HTC) (see Definitions section)

  2. Individual is male and is 18 years or older

  3. Individual has a confirmed diagnosis of moderate to severe Hemophilia B (congenital Factor IX deficiency) with **ALL** of the following:

     - History of laboratory confirmation of a plasma Factor IX (FIX) activity level ≤ 2%
     - Currently receiving Factor IX prophylaxis therapy (provider mush submit documentation of drug name, dose and frequency)
     - Current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes
     - Does NOT have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test

  4. Individual has received and completed **ALL** the following baseline tests before initiation of treatment and with continued monitoring of the individual as clinically appropriate:

     - Factor IX inhibitor test (within previous 3 months)
     - Liver function tests, total bilirubin and albumin (within previous 3 months)
     - Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests) have been done within the previous 12 months
     - Hepatic ultrasound and elastography

  5. Individual does **NOT** have **ANY** of the following:

     - Current or prior history of a factor IX inhibitor (positive test is ≥ 0.6 Bethesda Units (BU))
     - Hepatitis B or untreated Hepatitis C
     - HIV that is not controlled with anti-viral therapy (CD4+ count ≤ 200µL or viral load ≥ 20 copies/mL)
     - Prior gene therapy or is being considered for treatment with any other gene therapy
     - Current liver-related coagulopathy, hypoalbuminemia, persistent jaundice, or cirrhosis, portal hypertension, splenomegaly, hepatic encephalopathy, or hepatic fibrosis (see Definition Section)

- Significant dysfunction defined as **ANY** of the following:

  a. Alanine aminotransferase (ALT) > 2 times upper limit of normal
  b. Aspartate aminotransferase (AST) > 2 times upper limit of normal
  c. Alkaline phosphatase (ALP) > 2 times upper limit of normal
  d. Total bilirubin > 1.5 times upper limit of normal

6. The Attestation for Beqvez Treatment form (see below) has been signed by the physician (or designee)

Initial approval duration: One-time treatment per lifetime
The safety and effectiveness of repeat administration of Beqvez (fidanacogene elaparvovec-dzkt) have not been evaluated.

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

Required Outcomes Measurements:
- Baseline prophylactic factor use including name of product, dose, and frequency of administration
- Laboratory evaluations including:
  - Baseline and follow up liver health assessment
  - Baseline factor IX inhibitor testing and follow up factor IX inhibitor testing if the individual begins continuous prophylactic factor therapy after Beqvez administration
- Provider will submit documentation of any prophylactic factor therapy required after Beqvez administration including name of product, dose, and frequency of administration

➢ Beqvez (fidanacogene elaparvovec-dzkt) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

HEMGENIX (etranacogene dezaparvovec-drlb)

- **Criteria for initial therapy:** Hemgenix (etranacogene dezaparvovec-drlb) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a Hematologist at or in consultation with a Hemophilia Treatment Center (HTC) (see Definitions section)

2. Individual is male and is 18 years or older

3. Individual has a confirmed diagnosis of moderately severe or severe Hemophilia B (congenital Factor IX deficiency) with **ALL** of the following:

   - History of laboratory confirmation of a plasma Factor IX (FIX) activity level ≤ 2%
   - Currently receiving Factor IX prophylaxis therapy (provider mush submit documentation of drug name, dose and frequency)
   - Current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes

4. Individual has received and completed **ALL** the following baseline tests before initiation of treatment and with continued monitoring of the individual as clinically appropriate:

   - Factor IX inhibitor test (within previous 3 months)
   - Liver function tests and total bilirubin (within previous 3 months)
   - Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests) have been done within the previous 12 months
   - Hepatic ultrasound and elastography

5. Individual does **NOT** have **ANY** of the following:

   - Current or prior history of a factor IX inhibitor
   - Hepatitis B or untreated Hepatitis C
   - HIV that is not controlled with anti-viral therapy (CD4+ count ≤ 200µL)
   - Prior gene therapy or is being considered for treatment with any other gene therapy
   - Significant liver dysfunction defined as **ANY** of the following:

     a. Alanine aminotransferase (ALT) > 2 times upper limit of normal
     b. Aspartate aminotransferase (AST) > 2 times upper limit of normal
     c. Alkaline phosphatase (ALP) > 2 times upper limit of normal
     d. Total bilirubin > 2 times upper limit of normal

6. The Attestation for Hemgenix Treatment form (see below) has been signed by the physician (or designee)

Initial approval duration: One-time treatment per lifetime
The safety and effectiveness of repeat administration of Hemgenix (etranacogene dezaparvovec-drlb) have not been evaluated.

Approval conditions:
If an individual meets all coverage guideline criteria and is approved to receive treatment, the requesting provider attests and agrees to submit clinical outcomes data and information.

Required Outcomes Measurements:
- Baseline prophylactic factor use including name of product, dose, and frequency of administration
- Laboratory evaluations including:
  - Baseline and follow up liver health assessment
  - Baseline factor IX inhibitor testing and follow up factor IX inhibitor testing if the individual begins continuous prophylactic factor therapy after Hemgenix administration
- Provider will submit documentation of any prophylactic factor therapy required after Hemgenix administration including name of product, dose, and frequency of administration

➢ Hemgenix (etranacogene dezaparvovec-drlb) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Attestations for Beqvez or Hemgenix Treatment

Physician Name: _____

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Individual Name: _____ DOB**:** _____

Treatment requested: _____

- The Physician is responsible for filling out this form.
- All elements must be initialed, and the form must be signed by the Physician (or designee).
- Incomplete forms will be returned to acquire missing information, initial, signature, or date.
- Return completed form to BCBSAZ.

Physician Agreement:

- Physician to initial by each element and date and sign to show willingness to participate.
- Documentation may include, but is not limited to, chart notes, laboratory test results, claims records, and/or other information.

Initials:

_____ I verify that the patient will be closely followed and monitored for progression of disease

_____ I agree to submit clinical outcomes data and information

_____ I agree to submit baseline prophylactic factor use including name of product, dose and frequency of administration

_____ I agree to submit lab results including:
- Baseline and follow up liver health assessment testing
- Baseline Factor IX inhibitor testing and follow up Factor IX inhibitor testing if the individual begins continuous prophylactic factor therapy after gene therapy administration

_____ I agree to submit documentation of any prophylactic factor therapy required after gene therapy administration including name of product, dose, and frequency of administration

Provider (or designee) Signature: _____

Date: _____

Description:

Hemophilia B is an inherited X-linked genetic disorder primarily affecting males, though can occur spontaneously characterized by a deficiency in factor IX clotting activity. The diagnoses and frequency of bleeding episodes are related to the level of factor IX clotting activity. The normal range for factor IX

clotting activity is approximately 50-150%. Hemophilia B is categorized based on factor IX activity as mild (>5-40%), moderate (1-5%) and severe (<1%).

Treatment for acute bleeding episodes is plasma-derived or recombinant factor IX and should be initiated within an hour of symptom onset. Dosing is weight based and will depend on severity of bleeding or bleeding risks with an associated surgery or procedure. Prophylactic treatment with routine infusions of factor IX is standard of care in individuals with severe Hemophilia B. The goal is to maintain a trough factor IX activity level greater than 1% to prevent spontaneous bleeds and prevent chronic joint disease. Prophylaxis early in life has been associated with over a 90% reduction in joint bleeding rates, annualized joint bleeding rates below 3 per year and a significant reduction in joint deterioration and degenerative joint disease. Prophylaxis benefits include reduction of chronic pain, functional limitations, and disability, need for orthopedic surgery, hospitalization, emergency room visits and hospitalization.

Inhibitors to factor IX are documented in 1% to 3% of individuals with severe hemophilia B. These inhibitors can be associated with anaphylactic reactions to factor IX infusion and nephrotic syndrome. Treatment options include immune tolerance therapy, which can be challenging, or long-term bypassing therapy.

Beqvez (fidanacogene elaparvovec-dzkt) is indicated for the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who:
- Currently use factor IX prophylaxis therapy, or
- 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 indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:
- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes

Beqvez is an adeno-associated virus (AAV)-based gene therapy 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). A single intravenous infusion results in cell transduction and increase in circulating factor IX activity in patients with hemophilia B.

Hemgenix is an adeno-associated virus serotype 5 (AAV5) based gene therapy for a single intravenous infusion. AAV5 is a viral vector that is non-replicating. This gene therapy is designed to deliver a copy of a gene encoding the Padua variant of human coagulation Factor IX (hFIX-Padua). This results in cell transduction and increase in circulating Factor IX activity in individuals with hemophilia B.

Hemgenix was evaluated in 54 individuals in a prospective, open-label single-dose, single-arm, multi-national on-going study. Beqvez was studied in 60 individuals in two prospective, open-label single-dose,

single-arm, multi-national on-going studies. The primary study was in 45 males with baseline factor IX activity levels less than or equal to 2 percent. For both Beqvez and Hemgenix, individuals completed a 6 month lead-in for pre-study comparison of annualized bleed rate (ABR) on standard of care routine factor IX prophylaxis. They both demonstrated non-inferiority in ABR.

Gene therapy for hemophilia increases treatment options for, especially for individuals with severe hemophilia that are uncontrolled on standard-of-care prophylaxis. It is unknown whether gene therapy will provide a durable, long-term benefit or if the therapeutic effect will wane over time. Long-term safety for gene therapy is being explored in gene therapy registries and ongoing long-term clinical trials.

Definitions:

Hemophilia Treatment Center (HTC): HTCs are federally funded health clinics that utilize a comprehensive care model for individuals with hemophilia. They provide access to hematologists, orthopedists, physical therapists, nurses, lab services, and social workers and other mental health professionals. Their emphasis is in prevention services to help reduce or eliminate complications.
- CDC HTC Directory: https://www.cdc.gov/ncbddd/hemophilia/treatment.html

Symptoms and Severity of Hemophilia B:

Clinical Severity	Factor IX Clotting Activity	Symptoms if untreated
Severe	< 1%	▪ Frequent spontaneous bleeding ▪ Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions
Moderate	1-5 %	▪ Spontaneous bleeding rare ▪ Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions
Mild	> 5-40%	▪ No spontaneous bleeding ▪ Excessive and/or prolonged bleeding after major injuries, surgery or tooth extractions

For Beqvez: Hepatic fibrosis precluding use:
- FibroScan score >8 kPa units
- FibroTest/FibroSure >0.48
- AST-to-Platelet ratio >1

History:	Date:	Activity:
Pharmacy and Therapeutics Committee	08/15/24	Revisions to guideline: criteria, coding, resources
Pharmacy and Therapeutics Committee	02/15/24	Review with revisions: criteria, resources

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Pharmacy and Therapeutics Committee	11/16/23	Revision to criteria
Pharmacy and Therapeutics Committee	02/16/23	Approved Guideline
Clinical Pharmacist	02/16/23	Development

Coding:

HCPCS: J1411, C9399, J3590

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Resources:

Literature reviewed 02/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Beqvez (fidanacogene elaparvovec-dzkt) prescribing information, revised by Pfizer Inc 04/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 30, 2024.

2. Hemgenix (etranacogene dezaparvovec-drlb) prescribing information, revised by CSL Behring LLC 12/2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2023.

3. Hoots KH, Lewandowska M. Gene therapy and other investigational approaches for hemophilia. In: UpToDate, Shapiro AD, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on November 2, 2023. Accessed on November 29, 2023.

4. Hoots KH, Shapiro AD. Hemophilia A and B: Routine management including prophylaxis. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on September 14, 2023. Accessed on November 29, 2023.

5. Konkle BA, Huston H, Nakaya Fletcher S. Hemophilia B. 2000 Oct 2 [Updated 2017 Jun 15]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. https://www.ncbi.nlm.nih.gov/books/NBK1495/. Accessed on December 28, 2022.

6. Tice JA, Walton S, Herce-Hagiwara B, Fahim SM, et al. Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, December 22, 2022. https://icer.org/assessment/hemophilia-a-and-b-2022/. Accessed on December 28, 2022.

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Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html