# Molina Clinical Policy
# Beqvez (fidanacogene elaparvovec): Policy No. 458

**Last Approval: 06/12/2024**
**Next Review Due By: June 2025**

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

## OVERVIEW

**Fidanacogene elaparvovec (Beqvez**) is a systemically delivered gene therapy for the treatment of Hemophilia B. Beqvez is indicated for the treatment of hemophilia B in adults who currently use Factor IX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. Additionally, patients should not have a history of detectable antibodies to AAVRh74var per the Beqvez companion diagnostic assay.

**Hemophilia** is a bleeding disorder caused by deficiency of a coagulation factor. Patients with hemophilia can bleed spontaneously in the absence of recognized trauma and have delayed or recurrent bleeding prior to complete wound healing (Shah et al. 2022). There are multiple subtypes of hemophilia. Each subtype, either A, B, or C, are distinguished by the specific coagulation factor involved. A deficiency of factor VIII causes hemophilia A, deficiency of factor IX leads to hemophilia B, and loss of factor XI results in hemophilia C.

Hemophilia is most often inherited, but rare cases are acquired later in life. Hemophilia A and B are X-linked recessive bleeding disorders, while Hemophilia C follows an autosomal recessive inheritance pattern.

In the United States, hemophilia B incidence is approximately one in 30,000 male live births (CDC 2022). Hemophilia B represents an estimated 15% of hemophilia patients (FDA 2022). Hemarthrosis, the hallmark of severe hemophilia, is a major cause of disability, and reduced quality of life in patients with factor VIII or factor IX deficiency. Repeated hemarthrosis events result in hemophilic arthropathy, which is characterized by cartilage and bone degradation, bone remodeling, and progressive loss of function.

Factor levels in hemophilia (in hemophilia B an individual's percentage of factor IX) have traditionally been used to assess the severity of hemophilia although the clinical correlation is imperfect. Severe disease is defined by factor levels less than 1% of normal, according to factor level classifications (Refer to 'Supplemental Information' section for additional information on severity). In severe disease, recurrent bleeds typically result in arthropathy, joint contractures, and pseudo tumors. These events result in chronic pain, disability, and a diminished quality of life.

The current standard of care is either gene therapy for severe disease or Factor IX replacement therapy. Most patients with moderate to severe hemophilia B receive prophylactic Factor IX infusions. Gene therapy for the treatment of hemophilia B aims to shift the severest forms of hemophilia to a milder form or cure by increasing endogenous coagulation factor IX levels via the transfer of a functional IX gene. In the absence of longer-term data, however, the durability and safety of gene therapy remains unknown. As with Hemgenix, there is a theoretical risk of hepatocellular carcinoma secondary to viral vector integration into host DNA.

Beqvez is the second gene therapy for hemophilia B and was approved in April 2024. Hemgenix, the first gene therapy for hemophilia B was approved in 2022.

**Beqvez** adds a functional copy of the factor IX gene back to a person with hemophilia B via a viral vector. The viral vector is an adeno-associated virus (AAVRh74var). It is important to be aware a person with pre-existing antibodies

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to the viral vector could have significant adverse reactions to Beqvez. The assay called, nAbCyte™ Anti-AAVRh74var HB-FE Assay, is a companion diagnostic (CDx) used to determine pre-existing antibodies and is one component of patient eligibility for treatment with BEQVEZ.

Patients undergoing gene therapy may still require on-demand factor therapy, which should be accessible in cases such as trauma, surgery, and spontaneous bleeding.

## COVERAGE POLICY

**Fidanacogene elaparvovec (Beqvez**) for the treatment of hemophilia B may be considered medically necessary when **ALL** of the following criteria are met with relevant documentation:

1. A diagnosis of hemophilia B in an adult male, age 18 or older, but less than 65 years of age.
2. Documented moderately-severe to severe hemophilia B defined by Factor IX baseline residual level less than or equal to 2 IU/dL.
3. Member has a minimum of 50 exposure days to Factor IX replacement protein.
4. No presence or history of Factor IX inhibitors (Factor IX inhibitor titer test results required).
   NOTE: The definition of a positive inhibitor is a Bethesda titer of ≥0.6 BU (Bethesda units) for Factor IX.
5. No history of hypersensitivity to Factor IX replacement product
6. Member does not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test. For example, nAbCyte™ Anti-AAVRh74var HB-FE Assay, a companion diagnostic (CDx) test.
7. HIV
   a. Member is HIV negative documented by lab test within the past 3 months
   b. HIV positive AND well-controlled on antiretroviral therapy (CD4+ count > 200 $mm^3$ and or a viral load < 20 copies / ml)
8. Hepatitis B and C:
   a. Member does NOT have an active infection with hepatitis B or C virus documented by lab tests within the past 3 months:
      - Negative hepatitis B surface antigen, hepatitis B DNA negative and
      - Negative hepatitis C virus (HCV) RNA is negative
   b. For members with a history of hepatitis B or C exposure: Member is NOT currently using antiviral therapy for hepatitis B or C.
9. No history of significant liver or biliary disease
10. Member has had a liver evaluation within the last 30 days and the following lab values are ≤ 2 times the upper limit of normal:
    a. Alanine aminotransferase, Aspartate aminotransferase and alkaline phosphatase
    b. Total bilirubin ≤ 1.5 times the upper limit of normal
11. Liver elastography or ultrasound or FibroSURE test do not suggest liver fibrosis. FibroSURE test ≤ 0.48 is acceptable, FibroSURE test > 0.48 is suggestive of liver fibrosis.
12. Member has a hemoglobin level ≥ 11g/dl and platelets > 100,000 cells/uL
13. Creatinine ≤ 2mg/dL

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14. No history of conditions associated with increased thromboembolic risk

15. Member has not received, or is being considered for other gene therapy, or investigational cellular therapy for hemophilia.

## LIMITATIONS AND EXCLUSIONS

**QUANTITY LIMITATIONS: FDA approved dosing with one-time dose per lifetime.** Additional infusions of Beqvez will not be authorized.

**CONTINUATION OF THERAPY**
**Fidanacogene elaparvovec (Beqvez**) is indicated as a one-time infusion only. Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary.

There are no contraindications listed in the manufacturer's labeling at this time.

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

## SUMMARY OF MEDICAL EVIDENCE

Interim data from the phase III clinical trial BENEGENE-2 (NCT03861273) was used to support FDA approval of Beqvez. BENEGENE-2 is an ongoing prospective, open label single arm, multi-national study evaluating the efficacy of BeqVez for the treatment of moderately-severe to severe Hemophilia B. A total of 45 male individuals with moderately-severe to severe hemophilia B (FIX activity level < 2 IU/dL) received a single dose of Beqvez (5 x $10^{11}$ vg/kg of body weight). The participants were followed for a median of 2 years from the time of infusion. FIX activity level and ABR (annualized bleeding rate) were compared to the 6 months prior to Beqvez administration while on prophylactic FIX activity. The study will be completed after 6 years or 312 weeks of follow-up.

Key inclusion criteria were that participants had to be males, at least 18 years old, with a diagnosis of severe or moderately-severe congenital hemophilia B, currently on factor IX prophylaxis and exposure to Factor IX protein for at least 50 days. Key exclusion criteria included a history of Factor IX inhibitors or a positive Factor IX inhibitor test at screening, select liver screening laboratory test values over 2 times the upper limit of normal or history of hepatitis B or C or active infection (given the risk of potential hepatotoxicity), a positive HIV test that is not controlled with antiviral therapy, unstable liver or biliary disease, significant liver fibrosis, and previous gene therapy treatment.

The effectiveness was determined by reductions in the ABR of adult males. The primary endpoint was a non-inferiority test of annualized bleeding rates. Baseline ABR pre-treatment was 4.5 bleeds / year and post treatment bleeds were 2.5/year. The difference between the mean post Beqvez ABR and the baseline ABR was 2.1 bleeds / year which met the non-inferiority test success criterion.

The annualized FIX infusion rate was 58.8 before Beqvez treatment and 3.5 post Beqvez infusion. Six out of 45 patients (13%) had to re-start prophylactic FIX infusion post Rx. 64% of Rx pts had no bleeds post treatment compared with 29% during prophylaxis.

There were no serious adverse reactions reported in the Beqvez trial. 29 out of 45 subjects had transaminase elevations, 28 of which were treated with corticosteroids. No patients developed Factor IX inhibitors during the clinical studies.

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**Summary of Annualized Bleeding Rate and Bleeding Events (N=45) in BENGENE-2 Phase 3 clinical trial.** (Confidence intervals are presented in parenthesis separated by commas)

| | Baseline (Prospective Lead-in Period) | Post-BEQVEZ Efficacy Evaluation Period[a] |
|---|---|---|
| Median (range) of follow-up time (years) | 1.2 (0.6, 2.4) | 1.8 (0.2, 3.0) |
| Total follow-up time (person-years) | 59 | 83 |
| Median (min, max) ABR (bleeds/year)[b] | 1.3 (0.0, 53.9)[c] | 0.0 (0.0, 19.0) |
| Model derived mean ABR [bleeds/year] (95% CI)[b,d] | 4.5 (1.9, 7.2) | 2.5 (1.0, 3.9) |
| n (%) of patients without any bleeds | 13 (29%) | 27 (60%) |
| Total number of observed bleeds | 225 | 98 |
| Number of observed spontaneous bleeds (proportion of total bleeds) | 157 (70%) | 60 (61%) |
| Number of observed joint bleeds (proportion of total bleeds) | 184 (82%) | 71 (72%) |

ABR=Annualized Bleeding Rate for all bleeds (treated and untreated with factor IX, excluding procedural bleeds). CI = confidence interval.
a. Post-BEQVEZ efficacy evaluation period is from Week 12 (Day 82) to data cutoff. b. A total of 7 participants (16%) had used factor IX replacement products during the efficacy evaluation period for extended prophylaxis that confounded the treatment effect of BEQVEZ, with a median start time at 0.8 (range: 0.4 to 1.1) years. An ABR of 20 bleeds/year was imputed for the confounded periods. c. The results presented in this table included data on a participant with a baseline ABR of 53.9 bleeds/year, which disproportionately influenced the baseline ABR estimate. A post-hoc sensitivity analysis, excluding this participant, still met the non-inferiority study success criterion. d. Model-based ABR estimates from a repeated measures generalized linear model with negative binomial distribution and identity link function.

An uncontrolled phase 1, 2 trial (NCT02484092) was conducted to look at the safety and efficacy of fidanacogene in 10 males (18 to 53 years of age) with hemophilia B. In three of the participants Factor IX was used on demand and prophylactically in 7 participants. There were no serious adverse events, The trial demonstrated both safety (primary outcome) and Factor IX expression (secondary outcome). The mean expression level of Factor IX post fidanacogene treatment was 33.7 +- 18.5%. The exploratory outcome was mean ABR reduction which went from baseline at 11 events per year to 0.4 events per year after fidanacogene.

A 5-year follow-up study was reported Samelson-Jones in 2021. 15 patients were initially enrolled in a 52-week study, and followed thereafter for up to 5 years. No serious adverse events were reported. No reports of inhibitor development liver mass development or thrombotic events. Mean FIX activity levels were 22.8% at year 1, and 19.8% at year 5. No patients resumed FIX prophylaxis and ABR ranged from 0 to 0.9. A poster presentation in 2023 (Rasko 2023) reported 5-year follow-up liver health data from the phase 1 / 2 trial after Beqvez therapy. The most common findings were mild sustained elevations of alanine aminotransferase of uncertain etiology. One of the 10 participants in the long term follow-up study, developed a fatty liver. No elevations of alpha-fetoprotein.

## National and Specialty Organizations

**World Federation of Hemophilia (WFH)**
*Guidelines for the Management of Hemophilia 2020, 3rd edition*
The guidelines strongly advise that individuals with a severe phenotype of both hemophilia A and hemophilia B be on prophylaxis adequate to avoid all bleeding. Long-term prophylaxis is recommended as the standard of care, particularly in children, to prevent bleeding, hemarthrosis, and to improve quality of life. The prophylactic regimen should, whenever possible, be individualized for each patient based on bleeding phenotype, unique pharmacokinetics, and joint status. The guidelines do not specify a preference for recombinant over plasma-derived clotting factor concentrates and indicate that the selection between these product types should be determined based on availability, cost, and patient preferences.

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The guidelines address gene therapy in general, noting that 'Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies. This will require evaluation through long-term follow-up as part of clinical trials and registries.' The current 2020 guidelines include no specific recommendations for Beqvez

The World Federation of Hemophilia have not reviewed Beqvez for inclusion into its guidelines because Beqvez was only recently approved. Guidelines for Beqvez per NICE (National Institute for Health and Care excellence) are expected in August 2024.

The international consensus recommendations on the management of people with hemophilia B were published in 2022 (Hart 2022). Recommendations included making patients aware of the unpredictability of FIX expression level and duration of expression, and that clinicians should consider the specific geographic pattern of AAV seropositivity in directing their choice of gene therapy.

## SUPPLEMENTAL INFORMATION

Hemophilia B disease severity is classified as mild, moderate, or severe based on the plasma concentration of Factor IX (normal activity level 50%-150%):

- **Mild** is defined as factor IX activity > 5%-40% (> 0.05-0.4 units/mL), is usually diagnosed later in life, and is characterized by prolonged bleeding following major trauma or surgery.
- **Moderate** is defined as factor IX activity ≥1%-5% (0.01-0.05 units/mL), is usually diagnosed between age 5 and 6 years, and is characterized by bleeding following minor trauma but may present with spontaneous bleeding.
- **Severe** is defined as factor IX activity < 1% (< 0.01 units/mL), is usually diagnosed in the first 2 years of life and may present with spontaneous mild or life-threatening bleeding.

## CODING & BILLING INFORMATION

**CPT (Current Procedural Terminology)**

| Code | Description |
|---|---|
| **96413** | Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug |
| **96415** | Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure) |

**HCPCS (Healthcare Common Procedure Coding System)**

| Code | Description |
|---|---|
| **C9172** | Injection, fidanacogene elaparvovec-dzkt, per therapeutic dose (effective until 12/31/2024) |
| **J1414** | Injection, fidanacogene elaparvovecdzkt, per therapeutic dose (effective on 1/1/2025) |

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

**06/12/2024** New policy. IRO completed and policy approved by board certified hematologist May 30, 2024.

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