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# Fidanacogene elaparvovec-dzkt

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## Disclaimer

*Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.*

### Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Legislative Mandates

**EXCEPTION: For HCSC members residing in the state of Ohio**, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

## Coverage

Fidanacogene elaparvovec-dzkt (Beqvez™) **may be considered medically necessary** when **ALL** the following criteria are met:

1. Individuals ≥ 18 years of age and assigned male at birth; AND
2. Individual has a confirmed diagnosis of severe or moderately severe hemophilia B (congenital Factor IX deficiency) (See Table 1 in Policy Guidelines); **AND**
    a. Current use of Factor IX prophylaxis; OR
    b. Current or historical life-threatening hemorrhage; OR
    c. Repeated, serious spontaneous bleeding episodes; AND
3. Absence of Factor IX inhibitor, confirmed by Factor IX inhibitor titer testing; AND
4. Individual does **NOT** have any of the following:
    a. Significant liver disease (e.g., elevated alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase [ALT, AST, or ALP] greater than 2 times the upper limit of normal [ULN] or bilirubin greater than 1.5 times ULN);
    b. Active hepatitis B or C;
    c. Currently on antiviral therapy for hepatitis B or C;
    d. Serological evidence of human immunodeficiency virus (HIV-1 or HIV-2) with CD4 counts ≤ 200/$mm^3$;
    e. Prior gene therapy.

Fidanacogene elaparvovec-dzkt (Beqvez™) **is considered experimental, investigational, and/or unproven** for all other indications.

Repeat treatment of fidanacogene elaparvovec-dzkt (Beqvez™) **is considered experimental, investigational, and/or unproven.**

## Policy Guidelines

**Table 1. Hemophilia B Severity, FIX Activity Levels and Symptoms (2, 3)**

| Severity | Mild | Moderate | Severe |
|---|---|---|---|
| **FIX Activity** | ≥5% to 40% of normal | 1 to 5% of normal | <1% of normal |
| **Symptoms** | • Rare spontaneous bleeding.<br>• Excessive and/or prolonged bleeding after major injuries, surgery, or tooth extractions.<br>• May not be diagnosed until an injury, surgery or tooth | • Occasional spontaneous bleedings.<br>• Excessive and/or prolonged bleeding after minor injuries, | • Have at least monthly bleeds, most frequently in joints without preceding trauma. |

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| | extraction that results in prolonged bleeding.<br>• First episode may only occur in adulthood. | surgery, or tooth extractions. | |
| **Usual Age at Diagnosis** | Later in life, depending on hemostatic challenges. | Age <5-6 years | Age ≤2 years |
| **Estimated Prevalence** | 28% | 41% | 30% |

FIX: factor IX.

## Description

**Hemophilia B**

Hemophilia B is a recessive X-linked congenital bleeding disorder, caused by mutations in the F9 gene resulting in factor IX (FIX) being deficient, missing or functionally defective. It is the second most common coagulation factor deficiency. Because it is a X-linked recessive inheritance, hemophilia predominately affects males, but females can have FIX deficiency and female cases of hemophilia B, while less common than male cases, have been noted in the literature. Spontaneous and recurring hemarthroses cause progressive joint damage, gradually resulting in end-stage hemophiliac arthropathy. Arthritis, a common type of arthropathy, is highly prevalent in patients with hemophilia B, especially those with severe disease. (1)

Hemophilia B occurs in approximately 1 in 25,000 male births, with all races and ethnic groups affected equally. The severity of hemophilia B has generally been defined by factor levels. Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted. Hemophilia B may be characterized as severe, moderate, or mild based on factor level correlating with the disease pattern and summarized in Table 1 in Policy Guidelines above. (1)

<u>Diagnosis</u>

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. (3) 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 (and is thus relevant to hemophilia B) while the PT assay tests for factors I, II, V, VII and X. (1, 2, 3) In the event of an abnormal aPTT result, diagnosis of hemophilia B is established by a one-stage aPTT based FIX assay, which measures the patient's FIX activity level and thus confirms whether the patient has FIX deficiency and how severe it is. (1) Following the FIX assay, genetic testing is recommended to identify the specific disease-causing gene mutation and evaluate the risk of inhibitor development. (3) Diagnosis is usually at a younger

age among patients with the severe (≤2 years) or moderate (<5-6 years) form of the disorder compared with those with mild disease who are typically diagnosed later in life or in adulthood. (1)

Current Treatment

FIX replacement therapy is provided via one of two modalities: prophylaxis (regular replacement) or on demand (episodic). Primary prophylaxis consists of regular and continuous FIX replacement therapy in the absence of documented joint disease and is initiated before the age of 3 years and the second clinically evident joint bleed. In secondary prophylaxis, regular and continuous infusions are started after the patient has two or more joint bleeds before the onset of joint disease, typically at or after the age of 3 years. Tertiary prophylaxis is initiated after the onset of documented joint disease, usually in adulthood. (3)

As per the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia, the standard of care for patients with severe hemophilia B is FIX prophylaxis to prevent bleeding, with initiation early in life before the age of 3 years to prevent musculoskeletal complications from recurrent joint and muscle bleeds. The goal of prophylaxis has been to maintain trough levels of circulating FIX at >1% of normal at all times to prevent spontaneous bleeds; however, the evidence has increasingly shown that trough levels at 1 to 3% of normal are insufficient to prevent bleeds completely in people with hemophilia B, the result being that some clinicians prefer >3 to 5% as the target trough range. FIX prophylaxis requires regular and frequent IV FIX infusions and regular venous access. (3) The most serious complication of replacement therapy is inhibitor (antibody) development. FIX inhibitors are allogenic antibodies to FIX that reduce or eliminate the activity of FIX. It is estimated that less than 5% of patients with severe hemophilia B develop inhibitors following exposure to FIX replacement therapy. (1, 4)

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. Recombinant FIX preparations are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation, but these are not first-line therapy. All approved products are approved for the indications, control, and prevention of bleeding episodes and perioperative management. Rixubis, Alprolix, and Idelvion are approved for the additional indication of routine prophylaxis. The goal of maintaining FIX activity levels of at least 1% (routine prophylaxis) requires regularly scheduled FIX infusions. For routine prophylaxis, the labeled dosing frequency is twice a week for Rixubis, once every 7 to 10 days for Alprolix, and once every 7 days for Idelvion. The National Hemophilia Foundation (NHF) guidelines recommend recombinant over plasma-derived FIX concentrates as the preferred option. (1, 4)

**Regulatory Status**

Fidanacogene elaparvovec-dzkt (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. It received approval from the U.S. Food and Drug Administration (FDA) in April 2024 as a one-time single-dose intravenous infusion 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. (5)

## Rationale

This medical policy was developed in May 2024 and is based on the studies provided to the U.S. Food and Drug Administration for approval.

The efficacy of fidanacogene elaparvovec-dzkt (Beqvez) was evaluated in clinical study 1 (NCT03861273) which is an ongoing, prospective, open-label, single-arm, multi-national study. The study enrolled 45 adult male patients with moderately severe to severe hemophilia B (factor IX activity ≤2 IU/dL). 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 clinical study 1. Enrolled patients then received a single intravenous infusion of Beqvez at a dose of $5 \times 10^{11}$ vg/kg of body weight and entered a follow-up (FU) period of 6 years. Of the 45 patients, 41 completed at least 15 months of FU. The median FU of the 45 treated patients was 2.0 years (range: 0.4 to 3.2 years) from the time of infusion.

Only patients who were negative for pre-existing neutralizing antibodies to AAVRh74var capsid were eligible. Other key exclusion criteria included history of or current inhibitor to factor IX (≥0.6 Bethesda units), active hepatitis B or C infection, HIV infection with CD4 cell count ≤200 $mm^3$ or viral load >20 copies/mL, hypersensitivity to factor IX product, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase (ALT/AST/ALP) >2 times upper limit of normal (ULN), bilirubin >1.5 times ULN, unstable liver or biliary disease, and significant liver fibrosis.

Enrolled patients were 73% White, 16% Asian and 2.2% Black. The median age was 29 years (range: 18 to 62 years). A total of 13 (29%) and 15 (33%) patients had a history of hepatitis B and C, respectively. One (2%) patient was HIV positive.

The main efficacy outcome was a non-inferiority (NI) test of annualized bleeding rate (ABR) during the efficacy evaluation period (EEP), Week 12 (Day 82) to data cutoff following Beqvez treatment, compared with baseline ABR during the lead-in period. The ABR included treated and untreated bleeds, excluding procedural bleeds. The NI margin on the difference between the mean EEP ABR and the mean baseline ABR was 3.0 bleeds/year.

Table 2 summarizes the efficacy results. 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. An additional patient had intermittent exogenous factor IX use and had a higher ABR post Beqvez (5.0 bleeds/year) compared to baseline (1.2 bleeds/year) with a factor IX activity <5% (SynthASil assay) starting at 0.4 years.

**Table 2. Summary of Annualized Bleeding Rate and Bleeding Events (N=45)**

| | **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 of 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.

**Summary of Evidence**

Based on the clinical study reviewed by the U.S. Food and Drug Administration, fidanacogene elaparvovec-dzkt (Beqvez™) may be considered medically necessary for individuals ages 18 years and older, and assigned male at birth, for the treatment of moderate to severe hemophilia B when the criteria noted in the coverage are met. Fidanacogene elaparvovec-dzkt (Beqvez™) is considered experimental, investigational, and/or unproven for all other indications. Repeat treatment of fidanacogene elaparvovec-dzkt (Beqvez™) is considered experimental, investigational, and/or unproven.

**Practice Guidelines and Position Statements**

World Federation for Hemophilia (3)

In the World Federation for Hemophilia (WFH) guidelines, the preferred treatment strategy is pharmacologic treatment and exogenous FIX replacement by IV injection of recombinant FIX or human plasma-derived FIX concentrates is the recommended treatment of choice for patients with hemophilia B. (3)

National Bleeding Disorders Foundation (4)

The National Bleeding Disorders Foundation's (formerly the National Hemophilia Foundation's [NHF]) Medical and Scientific Advisory Council (MASAC) guidelines include the following recommendations:

- *MASAC Document 284 – MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System (April 11, 2024)*
  - Recombinant factor IX products are the recommended treatment of choice for patients with hemophilia B.
- *MASAC Document 267 – MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors (April 27, 2022)*
  - Prophylaxis should be initiated at an early age, ideally before age 3 years and prior to the second joint bleed; prophylaxis may be considered within the first six months of life to reduce occurrence of intracranial hemorrhage.
  - Prophylaxis should be individualized (by dose and or frequency adjustment) and sufficient to prevent all bleeds at all times.
  - Options for prophylaxis include plasma-derived or recombinant standard half-life factor, extended half-life factor and non-factor replacement.

United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) (6)

The UKHCDO issued the following guidelines on the use of prophylactic factor replacement for children and adults with hemophilia A and B:

- All children with severe hemophilia A or B (SHA or SHB) should receive primary prophylaxis. Grade 1A
- Primary prophylaxis should be considered for all children with baseline factor levels of 1–3 iu/dl. Grade 2C
- Prophylaxis should be offered to any person with hemophilia (PWH) who has sustained one or more spontaneous joint bleeds. Grade 2C
- Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B
- In a person with SH or MH with a baseline level 1–3 iu/dl, primary prophylaxis should be started before or immediately after the first joint bleed. This will usually be at the time of ambulation, around 12 months of age and certainly before 24 months. Grade 2C
- Following initial treatment of a spontaneous intracranial haemorrhage, prophylaxis should be commenced and continued long term. Grade 1C
- Recombinant factor VIII and factor IX (FVIII and FIX) extended half-life (EHL) products should be used according to published UKHCDO guidance and used only when they provide clear clinical benefit over standard half-life products. Grade 1C

The UKHCDO utilizes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature to evaluate levels of evidence and to assess the strength of recommendations.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

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| **CPT Codes** | None |
| **HCPCS Codes** | C9172, J1414, J3490, J3590 |

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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4. National Bleeding Disorders Foundation. Guidelines on care: MASAC Documents. Available at <https://www.bleeding.org> (accessed May 8, 2024).
5. FDA. Highlights of Prescribing Information Beqvez™ (Fidanacogene elaparvovec-dzkt). 4/2024. Available at <https://www.fda.gov> (accessed May 7, 2024).
6. Rayment R, Chalmers E, Forsyth K, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. Br J Haematol. Sept 2020; 190(5):684-695. PMID 32390158


## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
|---|---|
| **Date** | **Description of Change** |
| 09/15/2024 | New medical document. Fidanacogene elaparvovec-dzkt (Beqvez™) may be considered medically necessary for individuals ages 18 years and older, and assigned male at birth, for the treatment of moderate to severe hemophilia B when the criteria noted in the coverage are met. Fidanacogene elaparvovec-dzkt (Beqvez™) is considered experimental, investigational, and/or unproven for all other indications. Repeat treatment of fidanacogene elaparvovec-dzkt (Beqvez™) is considered experimental, investigational, and/or unproven. |