Gene Therapy for Hemophilia B

Medicare Advantage Medical Policy # 091
Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider etranacogene dezaparvovec (Hemgenix®)‡ or fidanacogene elaparvovec-dzkt (Beqvez™)‡ for the treatment of hemophilia B to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of etranacogene dezaparvovec (Hemgenix) or fidanacogene elaparvovec-dzkt (Beqvez) will be considered when all of the following patient selection criteria are met:

- Patient is 18 years of age or older; AND
- Provider attests that patient has severe or moderately severe hemophilia B as defined by a baseline plasma Factor IX (FIX) activity level ≤ 2% of normal (< 2 IU/dL); AND
- Patient is currently receiving FIX prophylaxis continuously for at least 2 months; AND
- Patient meets ONE of the following:
    - Patient has experienced a current or historical life-threatening hemorrhage (e.g., CNS hemorrhage) requiring treatment with on-demand Factor IX infusion; OR
    - Patient has experienced repeated, serious spontaneous bleeding episodes requiring treatment with on-demand Factor IX infusion (e.g., bleeds requiring hospitalization, recurrent spontaneous bleeds in a joint or deep muscle); AND
- Patient has received > 150 exposure days of treatment with Factor IX protein; AND
- Patient does NOT have a history of Factor IX inhibitors or a positive screen result of ≥ 0.6 Bethesda Units (BU) using the Nijmegen-Bethesda assay; AND
- Patient has received a liver health assessment including enzyme testing [ALT, AST, ALP, and total bilirubin] AND a hepatic ultrasound and elastography; AND
- There is no evidence of cirrhosis and liver function tests are all below two times the upper limit of normal (except for total bilirubin if caused by Gilbert syndrome); AND
- Patient meets the below antibody titer requirements based on the drug requested:
    - For Hemgenix requests, patient has been tested for anti-AAV5 antibodies and is deemed a suitable candidate for treatment (see Policy Guidelines section for information about anti-AAV5 levels in the pivotal trial of Hemgenix); OR
    - For Beqvez requests, patient does not have neutralizing antibodies to AAVRh74var capsid; AND

- Patient does NOT have a history of receiving any prior gene therapy and is not under consideration for treatment with another gene therapy for hemophilia B; AND
- Patient is HIV negative or has a controlled HIV infection (i.e., CD4 count > 200 cells per µL); AND
- Patient does NOT have an active hepatitis B and/or hepatitis C infection (i.e., negative HCV RNA and not currently using antiviral therapy for hepatitis B or C); AND
- Dose will not exceed the below limits based on the drug requested:
    - For Hemgenix requests: one lifetime dose of 2×10^{13} genome copies per kg based on current body weight (within the past 30 days) administered by IV infusion; OR
    - For Beqvez requests: one lifetime dose of 5×10^{11} genome copies per kg based on current body weight (within the past 30 days) administered by IV infusion.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of etranacogene dezaparvovec (Hemgenix) when the patient does not have moderate or severe hemophilia B, has not been receiving FIX prophylaxis for at least 2 months, has not received > 150 exposure days of treatment with FIX protein, has not been tested for anti-AAV5 antibodies, has a history of receiving a prior gene therapy or is being considered for another gene therapy for hemophilia B, has active HIV, hepatitis B, or hepatitis C infection to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of fidanacogene elaparvovec-dzkt (Beqvez) when the patient has not been receiving FIX prophylaxis for at least 2 months, has not received > 150 exposure days of treatment with FIX protein, has a history of receiving a prior gene therapy or is being considered for another gene therapy for hemophilia B to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of etranacogene dezaparvovec (Hemgenix) or fidanacogene elaparvovec-dzkt (Beqvez) when patient selection criteria are not met (except for those denoted above as **not medically necessary****) to be **investigational.***

Policy Guidelines

A list of federally designated hemophilia treatment centers can be found here: https://dbdgateway.cdc.gov/HTCDirSearch.aspx

Anti-AAV5 antibodies in clinical trials of Hemgenix

In the clinical studies of Hemgenix, preexisting neutralizing anti-AAV5 antibodies were assessed prior to treatment. The subject sub-group with detectable preexisting neutralizing anti-AAV5

antibodies up to titers of 1:678 showed mean Factor IX activity that was numerically lower compared to the subject sub-group without preexisting neutralizing anti-AAV5 antibodies. Subjects with and without preexisting neutralizing anti-AAV5 antibodies demonstrated hemostatic protection. In one subject 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. The principal investigators of the pivotal clinical trial determined that benefits and safety were observed in participants with predose AAV5 neutralizing antibody titers of less than 1:700.

Background/Overview

Hemgenix and Beqvez are both adeno-associated virus vector-based gene therapies indicated for the treatment of adults with Hemophilia B who currently use Factor IX (FIX) prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. Beqvez is only approved for patients without neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid while Hemgenix is approved regardless of the neutralizing antibody titer. Both products are administered via a single intravenous infusion containing a certain number of genome copies per kg of body weight. Hemgenix uses an adeno-associated virus (AAV5) to provide a copy of a gene encoding the Padua variant of human coagulation FIX to increase the circulating level of FIX. Beqvez uses the AAVRh74var capsid to introduce a functional copy of the high-activity FIX variant (FIX-R338L, hFIX Padua) to the hepatocytes. Prior to treatment with either product, patients must undergo testing for Factor IX inhibitors and a thorough liver health assessment.

Hemophilia B is a genetic bleeding disorder caused by missing or insufficient levels of blood Factor IX, a protein required to stop bleeding. The condition is a rare X-linked bleeding disorder that mainly impacts males. Around 6,000 patients have hemophilia B in the US. Symptoms include heavy or prolonged bleeding following an injury or after a medical procedure. Spontaneous bleeding events may also occur. Bleeding can be internal into joints, muscles, or organs. The disease can be classified as mild, moderate, or severe with the severity of disease typically dictated by the level of circulating FIX. Normal plasma levels of Factor IX range from 50-150%. Mild hemophilia B is characterized by FIX levels of 6-49%, moderate disease includes FIX levels of 1-5%, and severe disease is defined as FIX levels < 1%. Prior to approval of Hemgenix, Factor IX replacement products have been the mainstay of treatment and can be used routinely to prevent bleeding or on demand to treat bleeding episodes. The formation of inhibitors, which can render FIX products ineffective and be challenging to manage, is rarer in patients with severe hemophilia B (3% to 5% of patients) compared with hemophilia A (25% to 35% of patients).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Hemgenix was approved in November 2022 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 was approved in April 2024 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Hemgenix

The efficacy of Hemgenix was evaluated in a prospective, open-label, single-dose, single-arm, multi-national study (n=54). The study enrolled adult male subjects aged 19 to 75 years, with severe or moderately severe Hemophilia B, who received a single intravenous dose of 2×10^{13} genome copies/kg body weight of Hemgenix and entered a follow-up period of 5 years. The study is ongoing.

The 54 subjects prospectively completed a lead-in period of at least six months with the intent to receive standard of care routine Factor IX prophylaxis. These 54 subjects then received the indicated single intravenous dose of Hemgenix. Subjects were then followed up monthly until Month 12, and then at 6-month intervals until Year 5. For the efficacy evaluation, data up to 18 months post-treatment were used. Of the 54 subjects, 53 subjects completed at least 18 months of follow-up in the ongoing study. One subject with numerous cardiovascular and urologic risk factors, aged 75 years at screening, died of urosepsis and cardiogenic shock at Month 15 post-dose (at age 77 years) unrelated to treatment. Another subject received around 10% of the intended dose of Hemgenix due to an infusion-related hypersensitivity reaction.

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. All bleeding episodes, regardless of investigator assessment, were counted. Subjects were allowed to continue prophylaxis during Months 0 to 6. The estimated ABR during Months 7 to 18 after Hemgenix treatment was 1.9 bleeds/year with a 95% confidence interval of (1.0, 3.4) compared with an estimated mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio was 0.46 demonstrating non-inferiority of ABR during Months 7 to 18 compared to the lead-in period. Two

subjects were not able to stop routine prophylaxis after Hemgenix treatment. During Months 7 to 18, an additional subject received prophylaxis from Days 396-534 (approximately 20 weeks). It should be noted that patients with AAV5 neutralizing antibodies were included in the trial and had similar efficacy results to patients without neutralizing antibodies with the exception of one subject who had an anti-AAV5 antibody titer greater than 1:700. This subject did not have an increase in FIX activity.

Beqvez

The efficacy of Beqvez was evaluated in 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 $\leq$ 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 5×10^{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 ($\geq$ 0.6 Bethesda units), active hepatitis B or C infection, HIV infection with CD4 cell count $\leq$ 200 mm^3 or viral load > 20 copies/mL, hypersensitivity to factor IX product, ALT/AST/ALP > 2 times ULN, bilirubin > 1.5 times ULN, unstable liver or biliary disease, and significant liver fibrosis.

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 ABR included treated and untreated bleeds, excluding procedural bleeds. The non-inferiority margin on the difference between the mean EEP ABR and the mean baseline ABR was 3.0 bleeds/year. 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 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 non-inferiority 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% starting at 0.4 years.

References

1. Hemgenix [package insert]. CSL Behring. King of Prussia, PA. Updated May 2023.
2. Pipe SW, Leebeek FWG, Recht M., et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med 2023:388:706-18.
3. Hemgenix Drug Evaluation. Express Scripts. Updated December 2022.

4. Hemgenix New Drug Review. IPD Analytics. Updated December 2022.
5. Beqvez [package insert]. Pfizer laboratories Div Pfizer Inc. New York, NY. Updated May 2024.
6. Beqvez New Drug Review. IPD Analytics. Updated May 2024.

Policy History

Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025
02/18/2025 UM Committee review. New policy
Next Scheduled Review Date: 02/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No code
HCPCS	J1411, J1414
ICD-10 Diagnosis	D67

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.