LOUISIANA BLUE

Gene Therapy for Hemophilia B

Policy # 00846
Original Effective Date: 08/14/2023
Current Effective Date: 04/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), 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 Company may consider etranacogene dezaparvovec (Hemgenix®)‡ for the treatment of hemophilia B to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of etranacogene dezaparvovec (Hemgenix) 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
  *(Note: The requirement that the patient have severe or moderately severe disease is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is currently receiving FIX prophylaxis continuously for at least 2 months; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- 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
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- 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 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); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- 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
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is HIV negative or has a controlled HIV infection (i.e., CD4 count > 200 cells per µL); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- 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
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Dose will not exceed 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.

  Note: In addition to meeting coverage criteria, provider will need to attest and agree to provide the necessary clinical outcome information via the Value Based Administrator's (Evio) secure web portal for the purposes of tracking and monitoring patient medical status and treatment outcomes.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company 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.****

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 Company considers the use of etranacogene dezaparvovec (Hemgenix) 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 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.

Anti-AAV5 antibodies can also be assessed using an AAV5 neutralizing antibody (NAb) test. In this test, the AAV5 neutralizing antibody titer is determined using a software analysis that calculates the percent of neutralization for each serum dilution after subtraction of background activity and fits a curve to the neutralization profile. Results are reported as a percentage of neutralization rather than a ratio. Therapeutic efficacy of AAV5-mediated gene therapy has been achieved in humans with pre-existing anti-AAV5 NAbs up to 340.

Background/Overview

Hemgenix is an adeno-associated virus vector-based gene therapy 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. It is 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. Prior to treatment with Hemgenix, 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.

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 regulations, other plan medical policies, and accredited national guidelines.

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.

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. Majowicz A, Nijmeijer B, Lampen MH, et al. Therapeutic hFIX Activity Achieved after Single AAV5-hFIX treatment in Hemophilia B Patients and NHPs with Pre-existing Anti-AAV5 NABs. Mol Ther Methods Clin Dev. 2019 May 28;14:27-36.

Policy History

Original Effective Date: 08/14/2023
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07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. New policy.
07/02/2024	Medical Policy Committee review
07/10/2024	Medical Policy Implementation Committee approval. Updated criteria to remove upper age limit, clarify diagnosis and anti-AAV5 titer requirements, and remove requirement that Hemgenix be administered at a federally designated hemophilia treatment center.
10/03/2024	Medical Policy Committee review
10/08/2024	Medical Policy Implementation Committee approval. Added new product, Beqvez, to policy with criteria and background information. Title changed from "etranacogene dezaparvovec (Hemgenix®)" to "Gene Therapy for Hemophilia B."

Coding

The five character codes included in the Louisiana Blue 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.

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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 Delete code effective 01/01/2025: C9172 Delete code effective 04/01/2025: 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.

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

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company 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.