



Louisiana

etranacogene dezaparvovec (Hemgenix[®])

Policy # 00846

Original Effective Date: 08/14/2023

Current Effective Date: 08/14/2023

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 younger than 75 years of age; AND
*(Note: The requirement that the patient be younger than 75 years of age is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has severe or moderately severe hemophilia B as defined by a baseline plasma Factor IX (FIX) activity level $\leq 2\%$ of normal (< 2 IU/dL) (documentation required); 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

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- 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 a baseline anti-AAV5 antibody titer $\leq 1:700$; 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; AND
- All care, services, and administration of Hemgenix will be provided by a federally designated hemophilia treatment center (See Policy Guidelines Section for list of federally designated hemophilia treatment centers).

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*(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.)*

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 is older than 75 years of age, 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 a baseline anti-AAV5 titer >1:700, 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, or is being treated at a facility other than a federally designated hemophilia treatment center 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

List of federally designated hemophilia treatment centers can be found here: <https://dbdgateway.cdc.gov/HTCDirSearch.aspx>

Background/Overview

Hemgenix is an adeno-associated virus vector-based gene therapy that is 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 2×10^{13} genome copies per kg of body weight. It 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

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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 more rare 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 federal regulations, other plan medical policies, and accredited national guidelines.

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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.

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3. Hemgenix Drug Evaluation. Express Scripts. Updated December 2022.
4. Hemgenix New Drug Review. IPD Analytics. Updated December 2022.

Policy History

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07/06/2023 Medical Policy Committee review

07/12/2023 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 07/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT[®])[‡], copyright 2022 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
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

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- 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.

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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.

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.

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