

POLICY: Hemophilia – Gene Therapy – Hemgenix Utilization Management Medical Policy

- Hemgenix® (etranacogene dezaparvovec-drlb intravenous infusion – CSL Behring and uniQure)

EFFECTIVE DATE: 5/15/2023

LAST REVISION DATE: 02/26/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Hemgenix, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of adults with **hemophilia B** (congenital Factor IX deficiency) who: 1) currently use Factor IX prophylaxis therapy; or 2) have current or historical life-threatening hemorrhage; or 3) have repeated, serious spontaneous bleeding episodes.^{1,2} The recommended dose of Hemgenix is 2×10^{13} genome copies per kg of body weight given as a one-time (per lifetime) single dose as an intravenous infusion.¹

Disease Overview

Hemophilia B is a genetic bleeding disorder caused by missing or insufficient levels of blood Factor IX, a protein required to produce blood clots to halt bleeding.³⁻⁶ The condition is a rare X-linked bleeding disorder that mainly impacts males. Hemophilia B is four times less common than hemophilia A, which is caused by a relative lack of blood Factor VIII. Approximately 30,000 individuals are living with hemophilia in the US and hemophilia B accounts for around 15% to 20% of hemophilia cases, or around 6,000 patients. Symptoms include heavy or prolonged bleeding following an injury or after a medical procedure. Bleeding can also occur internally into joints, muscles, or internal organs. Spontaneous bleeding events may also occur. Complications in patients with hemophilia B include joint disease and hemarthrosis. Hemophilia B may be diagnosed when bleeding occurs in infancy or later in life for those with milder disease. There is a strong correlation between Factor IX levels and phenotypic expression of bleeding. Normal plasma levels of Factor IX range from 50% to 150%. The disease is classified based on reduced levels. Mild, moderate, and severe hemophilia B is characterized by Factor IX levels ranging from 6% up to 49%, 1% up to 5%, and <1%, respectively. Besides gene therapies for the treatment of hemophilia B, Factor IX products, both recombinant and plasma-derived, are used routinely to prevent bleeding or are given on-demand to treat bleeding episodes associated with hemophilia B.³⁻⁶ Hympavzi™ (marstacimab subcutaneous injection), a tissue factor pathway inhibitor antagonist, is also FDA approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ≥ 12 years of age with hemophilia B (congenital Factor IX deficiency) without inhibitors; it is also indicated for use in hemophilia A.⁷

Clinical Efficacy

The efficacy of Hemgenix was evaluated in a prospective, open-label, single-dose, single-arm, multinational pivotal study called HOPE-B that involved 54 adult males with moderately severe or severe hemophilia B (Factor IX levels $\leq 2\%$).¹ Patients prospectively completed a lead-in period of at least 6 months in which standard care routine Factor IX prophylaxis therapy was given. This was followed by a single intravenous dose of Hemgenix. Patients were permitted to continue Factor IX prophylaxis during Months 0 to 6 after dosing, if needed, until Factor IX levels were adequate. Prior to screening, patients had been on stable prophylactic therapy for at least 2 months and had greater than 150 exposure days of treatment with a Factor IX product.² Factor IX inhibitors (or a history), uncontrolled human immunodeficiency virus (HIV) infection, or advanced liver fibrosis prevented participation. Adequate

hepatic and renal function were required. The estimated mean annualized bleeding rate during Months 7 to 18 following Hemgenix treatment was 1.9 bleeds/year compared with 4.1 bleeds/year during the lead-in period (before Hemgenix administration).¹ At 18 months after treatment, Factor IX activity had increased by 34.3%.² The HOPE-B trial is ongoing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hemgenix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hemgenix as well as the monitoring required for adverse events and long-term efficacy, approval requires Hemgenix to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Hemgenix, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Hemgenix as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemgenix is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophilia B.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
 - A) Patient is male*; AND
 - B) Patient is ≥ 18 years of age; AND
 - C) Patient has not received a gene therapy for hemophilia B in the past **[verification in claims history required]**; AND

Note: If no claim for Hemgenix or Beqvez (fidanacogene elaparvovec-dzkt intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Hemgenix or Beqvez.

 - D) Patient has moderately severe or severe hemophilia B as evidenced by a baseline (without Factor IX replacement therapy) Factor IX level $\leq 2\%$ of normal **[documentation required]**; AND
 - E) Patient meets ONE of the following (i, ii, or iii):

- i. According to the prescribing physician, the patient has a history of use of Factor IX therapy for ≥ 150 exposure days; OR
- ii. Patient meets BOTH of the following (a and b):
 - a) Patient has a history of life-threatening hemorrhage; AND
 - b) On-demand use of Factor IX therapy was required for this life-threatening hemorrhage; OR
- iii. Patient meets BOTH of the following (a and b):
 - a) Patient has a history of repeated, serious spontaneous bleeding episodes; AND
 - b) On-demand use of Factor IX therapy was required for these serious spontaneous bleeding episodes; AND

F) Patient meets BOTH of the following (i and ii):

- i. Factor IX inhibitor titer testing has been performed within the past 30 days **[documentation required]**; AND
- ii. Patient is negative for Factor IX inhibitors **[documentation required]**; AND

G) Patient meets BOTH of the following (i and ii):

- i. Patient does not have an active infection with hepatitis B virus or hepatitis C virus **[documentation required]**; AND
- ii. Patient is not currently receiving antiviral therapy for a prior hepatitis B virus or hepatitis C virus exposure **[documentation required]**; AND

H) According to the prescribing physician, the patient does not have uncontrolled human immunodeficiency virus infection; AND

I) Patient has undergone liver function testing within the past 30 days and meets ALL of the following (i, ii, iii, and iv):

- i. Alanine aminotransferase level is \leq two times the upper limit of normal **[documentation required]**; AND
- ii. Aspartate aminotransferase level is \leq two times the upper limit of normal **[documentation required]**; AND
- iii. Total bilirubin level is \leq two times the upper limit of normal **[documentation required]**; AND
- iv. Alkaline phosphatase level is \leq two times the upper limit of normal **[documentation required]**; AND

J) Patient does not have evidence of advanced liver impairment and/or advanced fibrosis; AND

K) Within the past 30 days, the platelet count was $\geq 50 \times 10^9/L$ **[documentation required]**; AND

L) Within the past 30 days, patient meets ONE of the following (i or ii):

- i. Patient has an estimated creatinine clearance $\geq 30 \text{ mL/min}$ **[documentation required]**; OR
- ii. Creatinine level is \leq two times the upper limit of normal **[documentation required]**; AND

M) The medication is prescribed by a hemophilia specialist physician; AND

N) Current patient body weight has been obtained within the past 30 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose (kit) of Hemgenix to provide for a one-time (per lifetime) single dose of 2×10^{13} genome copies per kg of body weight by intravenous infusion **[verification required]**. Table 1 provides the kit size and the National Drug Codes (NDCs).

* Refer to the Policy Statement.

Dosing. The recommended dose of Hemgenix is a one-time (per lifetime) single dose of 2×10^{13} genome copies per kg of body weight by intravenous infusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemgenix is not recommended in the following situations:

- Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the pivotal study.
- Patient with a History of Factor IX Inhibitors.** A history of Factor IX inhibitors was a reason for patient exclusion in the pivotal trial.
- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Table 1. Hemgenix Multi-Vial Kits.¹

| Total Number of Vials per Kit | Patient Body Weight | Total Volume per Kit | NDC Number |
|-------------------------------|---------------------|----------------------|--------------|
| 10 | 46 to 50 kg | 100 | 0053-0100-10 |
| 11 | 51 to 55 kg | 110 | 0053-0110-11 |
| 12 | 56 to 60 kg | 120 | 0053-0120-12 |
| 13 | 61 to 65 kg | 130 | 0053-0130-13 |
| 14 | 66 to 70 kg | 140 | 0053-0140-14 |
| 15 | 71 to 75 kg | 150 | 0053-0150-15 |
| 16 | 76 to 80 kg | 160 | 0053-0160-16 |
| 17 | 81 to 85 kg | 170 | 0053-0170-17 |
| 18 | 86 to 90 kg | 180 | 0053-0180-18 |
| 19 | 91 to 95 kg | 190 | 0053-0190-19 |
| 20 | 96 to 100 kg | 200 | 0053-0200-20 |
| 21 | 101 to 105 kg | 210 | 0053-0210-21 |
| 22 | 106 to 110 kg | 220 | 0053-0220-22 |
| 23 | 111 to 115 kg | 230 | 0053-0230-23 |
| 24 | 116 to 120 kg | 240 | 0053-0240-24 |
| 25 | 121 to 125 kg | 250 | 0053-0250-25 |
| 26 | 126 to 130 kg | 260 | 0053-0260-26 |
| 27 | 131 to 135 kg | 270 | 0053-0270-27 |
| 28 | 136 to 140 kg | 280 | 0053-0280-28 |
| 29 | 141 to 145 kg | 290 | 0053-0290-29 |
| 30 | 146 to 150 kg | 300 | 0053-0300-30 |
| 31 | 151 to 155 kg | 310 | 0053-0310-31 |
| 32 | 156 to 160 kg | 320 | 0053-0320-32 |
| 33 | 161 to 165 kg | 330 | 0053-0330-33 |
| 34 | 166 to 170 kg | 340 | 0053-0340-34 |
| 35 | 171 to 175 kg | 350 | 0053-0350-35 |
| 36 | 176 to 180 kg | 360 | 0053-0360-36 |
| 37 | 181 to 185 kg | 370 | 0053-0370-37 |
| 38 | 186 to 190 kg | 380 | 0053-0380-38 |
| 39 | 191 to 195 kg | 390 | 0053-0390-39 |
| 40 | 196 to 200 kg | 400 | 0053-0400-40 |
| 41 | 201 to 205 kg | 410 | 0053-0410-41 |
| 42 | 206 to 210 kg | 420 | 0053-0420-42 |
| 43 | 211 to 215 kg | 430 | 0053-0430-43 |

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|----|---------------|-----|--------------|
| 44 | 216 to 220 kg | 440 | 0053-0440-44 |
| 45 | 221 to 225 kg | 450 | 0053-0450-45 |
| 46 | 226 to 230 kg | 460 | 0053-0460-46 |
| 47 | 231 to 235 kg | 470 | 0053-0470-47 |
| 48 | 236 to 240 kg | 480 | 0053-0480-48 |

NDC – National Drug Code.

REFERENCES

1. Hemgenix® intravenous infusion [prescribing information]. King of Prussia, PA; Kankakee, IL; and Lexington, MA: CSL Behring and uniQure; November 2022.
2. Pipe SW, Leebeek FWG, Recht M, et al. Gene therapy with etranacogene daxaparvovec for hemophilia B. *N Engl J Med.* 2023;388:706-718.
3. National Bleeding Disorders Foundation. Hemophilia B. An overview of symptoms, genetics, and treatments to help you understand hemophilia B. Available at: <https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b>. Accessed on February 28, 2025.
4. Sidonio RF, Malec L. Hemophilia (Factor IX deficiency). *Hematol Oncol Clin N Am.* 2021;35:1143-1155.
5. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet.* 2021;397:630-640.
6. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin N Am.* 2022;36:797-812.
7. Hympavzi™ subcutaneous injection [prescribing information]. New York, NY: Pfizer; October 2024.

HISTORY

| Type of Revision | Summary of Changes | Review Date |
|------------------|---|-------------|
| New Policy | -- | 01/11/2023 |
| Annual Revision | <p>Hemophilia B: An overview of the changes are described below.</p> <ul style="list-style-type: none"> • The documentation requirement was removed regarding the criterion that the “Patient does not have evidence of advanced liver impairment and/or advanced fibrosis”. • The following criteria were removed which stated that after the Hemgenix infusion, the physician attests that the following will be performed: 1) liver enzyme testing to monitor for liver enzyme elevations will be done at least weekly for the first 3 months and periodically thereafter; AND implementing a course of corticosteroids will be considered if the patient experiences clinically relevant increases in alanine aminotransferase levels; 2) the patient will undergo monitoring for Factor IX activity at least weekly for the first 3 months and periodically thereafter; and 3) the patient with preexisting risk factors for hepatocellular carcinoma will receive abdominal ultrasound screenings and be monitored at least annually for alpha fetoprotein elevations in the 5 years following receipt of Hemgenix. • The requirement for the specialist physician was changed from “physician who specializes in hemophilia” to “hemophilia specialist physician”. • The criterion regarding a current patient body weight be obtained within 30 days was moved to a separate criterion. Previously, this requirement was combined with the Dosing. • Dosing was clarified with emphasis that Hemgenix is given as a “single dose”. Also, “documentation required” was replaced with “verification required”. A related sentence was added to the Policy Statement that verification of the appropriate weight-based dosing is required by the Medical Director. • Regarding use of Hemgenix in the past, the phrase “verification required by prescriber” was changed to “verification in claims history required”. A qualifier was added to reflect that this requirement applies only if a claims history is available; this change was also reflected in the related Policy Statement. Wording regarding “prescriber must attest” was changed to “prescribing physician confirms” regarding the verification that the patient has not previously received Hemgenix. Also, in the Note, the following statement was removed as it is duplicative: verify through claims history that the patient has not previously received Hemgenix. | 02/28/2024 |

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|-------------------|---|------------|
| | <ul style="list-style-type: none"> The phrase “prescriber attests” was removed from the requirement that “prophylactic therapy with Factor IX will not be given after Hemgenix administration once adequate Factor IX levels have been achieved” as well as the to the requirement regarding “patient does not have another coagulation disorder, besides hemophilia B”. In the requirement that Factor IX inhibitor titer testing has been performed “within 30 days”, the phrase “before receipt of Hemgenix” was removed. The phrase regarding liver “health assessment” was changed to liver “function testing”. For the requirement that the patient does not have uncontrolled human immunodeficiency virus, the word “infection” was added after this phrase. <p>Conditions Not Recommended for Approval: The condition of “Prior Receipt of Gene Therapy” was added.</p> | |
| Selected Revision | <p>Hemophilia B:</p> <ul style="list-style-type: none"> Regarding use of Hemgenix in the past, the criterion was changed due to the recent approval of Beqvez (fidanacogene elaparvovec intravenous infusion) for this indication. It now states that the patient has not received “a gene therapy for hemophilia B” in the past. It was added that there should not be claims present for Beqvez and that if claims history is not available, the prescribing physician confirms that the patient has not previously received Beqvez (previously, this only addressed Hemgenix). The option of approval was removed that the patient has been receiving routine prophylaxis with Factor IX therapy continuously for ≥ 2 months. The requirement that the patient does not currently have an inhibitor to Factor IX was reworded to state that the patient is negative for Factor IX inhibitors. The caveat of “According to the prescribing physician” was added to the requirement that the patient does not have uncontrolled human immunodeficiency virus infection; the documentation requirement was removed from this requirement; and the Note that addressed specific laboratory factors was removed. The requirement that within 30 days the patient has an estimated creatinine clearance ≥ 30 mL/min AND that the creatinine level is \leq two times the upper limit of normal was changed to having to meet <u>one</u> of these elements (not both). <p>The requirement that the patient does not have another coagulation disorder, besides hemophilia B, was removed.</p> | 05/15/2024 |
| UCare P&T Review | Policy reviewed and approved by UCare P&T committee. Annual review process | 09/16/2024 |
| Annual Revision | <p>Hemophilia B: The requirement that the patient does not have a history of Factor IX inhibitors (with documentation required) was removed from this section. The requirement that prophylactic therapy with Factor IX will not be given after Hemgenix administration once adequate Factor IX levels have been achieved was removed, along with the related Note. The Note that provides examples of advanced liver impairment and/or advanced fibrosis was removed. However, the criterion that the patient does not have evidence of advanced liver impairment and/or advanced fibrosis remains.</p> <p>Conditions Not Recommended for Approval: The condition of “Patient with a History of Factor IX Inhibitors” was added to this section. Previously, this was in a criterion related to the diagnosis of hemophilia B.</p> | 02/26/2025 |
| UCare P&T Review | Policy reviewed and approved by UCare P&T committee. Annual review process | 09/15/2025 |