Drug Coverage Policy

Effective **Date..... 3/27/2025**
Coverage Policy Number.....IP0535
Policy Title.....Hemgenix

Hemophilia – Gene Therapy – Hemgenix

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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 ≤ 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.

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POLICY STATEMENT
Prior Authorization is recommended for 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.

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.

Hemgenix is considered medically necessary when the following criteria are met:

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, O, and P):
   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 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 ≤ 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 ALL of the following (i, ii, and iii):
      i. Factor IX inhibitor titer testing has been performed within 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 30 days and meets ALL of the following (i, ii, iii, and iv):
      i. Alanine aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND
      ii. Aspartate aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND

iii. Total bilirubin level is ≤ two times the upper limit of normal **[documentation required]**; AND
iv. Alkaline phosphatase level is ≤ 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 30 days, the platelet count was ≥ 50 x 10^9/L **[documentation required]**; AND
L. Within 30 days, patient meets ONE of the following (i or ii):
   i. Patient has an estimated creatinine clearance ≥ 30 mL/min **[documentation required]**; OR
   ii. Creatinine level is ≤ two times the upper limit of normal **[documentation required]**; AND
M. The medication is prescribed by a hemophilia specialist physician; AND
N. Current body weight has been obtained within 30 days **[documentation required]**; AND
O. If criteria A through O are met, approve one dose (kit) of Hemgenix to provide for a one-time (per lifetime) single dose of 2 x 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 x 10^{13} genome copies per kg of body weight by intravenous infusion.

Hemgenix for any other use is considered not medically necessary including the following (this list may not be all inclusive; criteria will be updated as new published data are available.

1. **Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the pivotal study.

2. **Patient with a History of Factor IX Inhibitors.** A history of Factor IX inhibitors was a reason for patient exclusion in the pivotal trial.

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
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.

Coding Information

Note:
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose

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 dexaparvovec 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 18, 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.

Type of Revision	Summary of Changes	Date
Annual Revision	The following changes were made: **Hemophilia B:** An overview of the changes is described below. 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 to "hemophilia specialist physician." The criterion regarding a current patient body weight be obtained within 30 days was moved to a separate criterion. Dosing was clarified with emphasis that Hemgenix is given as a "single dose." Wording changed to "prescribing physician confirms" regarding the verification that the patient has not previously received Hemgenix. 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."	6/1/2024

	For the requirement that the patient does not have uncontrolled human immunodeficiency virus, the word "infection" was added after this phrase. **Conditions Not Covered:** The condition of "Prior Receipt of Gene Therapy" was added.	
Selected Revision	**Hemophilia B:** 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 ≤ two times the upper limit of normal was changed to having to meet <u>one</u> of these elements (not both). The requirement that the patient does not have another coagulation disorder, besides hemophilia B, was removed.	6/6/2024
Annual Revision	**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	3/27/2025

	removed. However, the criterion that the patient does not have evidence of advanced liver impairment and/or advanced fibrosis remains. **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.	

The policy effective date is in force until updated or retired.