MEDICAL COVERAGE POLICY	
SERVICE:	**Etranacogene dezaparvovec (Hemgenix®)**
Policy Number:	**312**
Effective Date:	**11/01/2024**
Last Review:	**08/12/2024**
Next Review:	**08/12/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Etranacogene dezaparvovec (Hemgenix®)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Determination: Baylor Scott & White Health Plan (BSWHP) may consider etranacogene dezaparvovec (Hemgenix®) medically necessary for the treatment of members with Hemophilia B (congenital factor IX deficiency) when ALL of the following criteria are met.

1. Member is 18 years of age or older **AND**
2. Documentation of moderately severe or severe hemophilia B as evidenced by a baseline (without FIX replacement therapy) FIX level of ≤ 2% of normal **AND**
3. Medication is prescribed by a physician who specializes in hemophilia **AND**
4. Meets one of the following criteria:
    a. Both of the following:
        i. Documentation of receiving routine prophylaxis with FIX therapy continuously for at least 2 months **AND**
        ii. According to the prescriber, has at least a 150-exposure day history of FIX therapy

    OR

    b. Both of the following:
        i. History of life-threatening hemorrhage **AND**
        ii. On-demand use of FIX therapy was required for this life-threatening hemorrhage

    OR

    c. Both of the following:
        i. History of repeated, serious spontaneous bleeding episodes **AND**

   ii. On-demand use of FIX therapy was required for these serious spontaneous bleeding episodes

AND

5. Member has adequate liver function as defined by **ONE** of the following:
   a. Both of the following
      i. Alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase [ALT, AST, or ALP] less than 2 times the upper limit of normal [ULN] **AND**
      ii. Bilirubin less than 1.5 times ULN

      OR
   b. In the presence of sustained liver enzyme elevations, attestation by a consulting hepatologist documenting eligibility to receive Hemgenix

   AND
6. Member meets one of the following
   a. Patient is not HIV positive **OR**
   b. Patient is HIV positive and is virally suppressed (< 200 copies of HIV per mL)

   AND
7. Member does **NOT** meet any of the following:
   a. AAV5 antibodies titer ≥1:678
   b. FIX inhibitors
   c. Active infection with hepatitis B or C virus at screening
   d. Current use of antiviral therapy for Hepatitis B or C
   e. Prior gene therapy

BSWHP considers repeat administration of etranacogene dezaparvovec experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers etranacogene dezaparvovec to be experimental and investigational for all other indications.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:
Hemophilia B is a rare inherited X-linked coagulation disorder. It is caused by mutations in the *F9* gene that prevent adequate production of coagulation factor IX (FIX), a protein essential for blood clot formation. Decreased levels of FIX result in prolonged bleeding that may occur spontaneously or after a traumatic event. The severity of symptoms depends on the degree of FIX deficiency:

Severity	**FIX Plasma Levels** (percent of normal)	**Common Symptoms**

Mild	6 - 49 %	Prolonged bleeding usually presenting only after significant trauma or surgery. Diagnosis is often made incidentally.
Moderate	1 - 5 %	Prolonged bleeding usually presenting after trauma, injury, dental work, or surgery. Recurrent joint bleeding may be present in up to 25% of cases. Diagnosis is usually made in late childhood or adulthood.
Severe	< 1 %	Frequent spontaneous bleeding presenting during infancy when disease is most often diagnosed. Bleeding into joints and muscles is common and can lead to intense pain, immobility, and permanent damage if left untreated. Occult bleeding into organs may also occur.

More than 6000 people are living with hemophilia B in the United States. A recent study conducted by the Centers for Disease Control and Prevention (CDC) found that a majority of patients with hemophilia B receive care at a specialized hemophilia treatment center; 70% of the 5106 patients with hemophilia B who received care at a hemophilia treatment center between 2012 and 2018 had moderate or severe disease.

The mainstay of treatment for hemophilia B is replacement of FIX with intravenous infusions of exogenous FIX recombinant or plasma-derived concentrate products. This therapy may be given as needed to treat a bleeding episode (episodic therapy) or routinely to help prevent bleeding episodes and mitigate further damage to joints and organs (prophylactic therapy).

Routine prophylactic therapy to reduce risk for bleeding and ensuing complications is the standard of care for patients with severe or moderate hemophilia B. Prophylaxis is generally effective but has several significant drawbacks. FIX replacement therapy is not a cure. Patients are dependent upon burdensome dosing schedules and monitoring protocols that make adherence to therapy a major challenge. In addition, 3% to 5% of patients with severe hemophilia B develop neutralizing antibodies (inhibitors) to exogenous FIX replacement products. New approaches to the treatment of hemophilia B are needed that address the underlying cause of FIX deficiency and eliminate or reduce dependence on prophylactic therapy. Etranacogene dezaparvovec (Hemgenix) is an FIX gene transfer product that was developed to address this need.

Etranacogene dezaparvovec (Hemgenix; CSL Behring) is a recombinant gene transfer therapy product designed to help patients with hemophilia B produce sufficient plasma levels of endogenous coagulation factor IX (FIX). The main therapeutic goal is long-term expression of FIX at levels steady enough to eliminate the need for routine prophylactic replacement therapy with exogenous FIX products. It is indicated for the treatment of adults with hemophilia B (congenital factor IX deficiency)

who currently use factor IX prophylaxis therapy, have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

Etranacogene dezaparvovec consists of a harmless adeno-associated virus 5 (AAV5) vector that delivers a highly functional variant of the *F9* gene (FIX-Padua) to the patient's liver, where FIX is produced. It is administered as single-dose intravenous infusion.

Researchers created etranacogene dezaparvovec to deliver the FIX-Padua variant, which provides clotting activity 6 to 8 times greater than that seen with the standard copy. It is the first gene transfer therapy for hemophilia B to be approved by the U.S. Food and Drug Administration (FDA). Pfizer has developed a competing product, fidanacogene elaparvovec-dzkt (Beqvez), that utilizes similar technology and received FDA approval April 2024. These gene transfer therapies will presumably compete with commercially available FIX replacement products indicated for routine prophylactic therapy.

The pivotal HOPE-B trial was published in February 2023. Etranacogene dezaparvovec was found to be superior to FIX prophylaxis therapy in patients with severe and moderately severe hemophilia B. Etranacogene dezaparvovec appears to be a promising new therapy for severe and moderately severe hemophilia B, but longer-term results in a larger patient population are needed to determine if the treatment effect is durable beyond 1.5 to 3 years.

HOPE-B was an open-label phase III study at 33 sites in the United States, Europe, and United Kingdom that evaluated etranacogene dezaparvovec in 54 men aged ≥ 18 years with inherited severe or moderately severe hemophilia B with FIX plasma levels ≤ 2%. Patients were on physician-recommended stable continuous FIX prophylaxis for a lead-in period of at least 6 months, during which all bleeding events were recorded. After lead-in, they received a single intravenous dose of etranacogene dezaparvovec at 2 × 1013 genome copies/kilogram. Patients with a history of FIX inhibitor use, advanced liver fibrosis, or uncontrolled human immunodeficiency virus (HIV) infection were excluded. The mean patient age was 41.5 ± 15.8 years. At the time of diagnosis, 44 (81%) patients had severe hemophilia B, and 10 (19%) were classified as moderately severe.

The primary endpoint was a noninferiority analysis of annualized bleeding rate based on all bleeding episodes that compared bleeding rate during the 52 weeks after stable FIX expression with the lead-in bleeding rate. Stable FIX expression was defined as months 7 through 18, after all participants who received glucocorticoid therapy discontinued it at 6 months. Noninferiority was defined as an upper limit of two-sided 95% Wald confidence interval (CI) of the annualized bleeding rate ratio that was less than the noninferiority margin of 1.8. Key secondary endpoints included FIX activity at 18 months after treatment, as well as superiority, number of infusions of FIX replacement therapy, and safety.

The primary endpoint was met: etranacogene dezaparvovec was noninferior and superior to FIX prophylaxis. The annualized bleeding rate decreased from the lead-in period rate of 4.19 (95% CI, 3.22-

5.45) to 1.51 (95% CI, 0.81-2.82) during months 7 to 18 after treatment; the rate ratio was 0.36 (95% Wald CI, 0.20-0.64; *P*<0.001).

Key secondary outcomes included the following:

- FIX activity increased from baseline by a least-squares mean of 34.3% (95% CI, 29.5-39.1)
- Mean use of FIX prophylaxis per patient decreased by 248,825 IU per year from lead-in to post-treatment period (*P*<0.001)
- Annualized FIX replacement infusion rate per patient decreased from 72.5 (95% CI, 63.6-82.7) infusions during the lead-in period to 2.5 (95% CI, 0.92-6.96) infusions post-treatment (*P*<0.001)
- Substantial reduction in annualized rates of spontaneous bleeding (71%) and joint bleeding (78%) from lead-in period to post-treatment period.
- No serious treatment-related adverse events occurred. However, one patient had an adverse hypersensitivity reaction after a partial dose during infusion, and did not receive the full dose.

Long term outcomes were reported at the American Society of Hematology Annual Meeting. 52 out of 54 patients had follow up of 36 months (3 years). The endogenous FIX activity level (ie. in the absence of exogenous FIX exposure) of participants was reported: mean±SD (median; range)

- 41.5 IU/dL ±21.7 (39.9; 5.9-113, n=50) at Year 1,
- 36.7 IU/dL ±19.0 (33.9; 4.7-99.2, n=50) at Year 2, and sustained at
- 38.6 IU/dL ±17.8 (36.0; 4.8-80.3, n=48) at Year 3 post-treatment.

Total number of bleeds (all types) were 136 during the ≥6-month lead-in period and decreased to 55 during Year 1, 48 during Year 2, and 37 during Year 3 post-treatment. Median [range] bleeds per participant decreased from 2.0 [0-10] during the lead-in period and remained stable to 0.0 [0-4] during Year 1, 0.0 [0-10] during Year 2, and 0.0 [0-8] during Year 3. Superior bleeding protection was in line with the level of transgene-derived endogenous FIX expression.

At 3 years post-treatment, 51 (94%) remained free of continuous FIX prophylaxis. One participant who lacked efficacy (highest AAV5 NAbs titer of 1:3212) and 1 who received a 10% partial dose of treatment did not discontinue prophylaxis; 1 participant eventually had his FIX levels declined to 2-5% range; his bleeding phenotype returned, and he resumed prophylaxis per protocol at month 30 post-treatment. During Year 2 and Year 3 post-treatment, 37 (70%) and 39 (75%) participants received no FIX infusion, respectively. Overall mean annualized FIX consumption decreased by 96% over 3 years post-treatment compared to the ≥6-month lead-in period (–246,763 IU/kg/participant, including those receiving FIX prophylaxis post-treatment; P<0.0001).

During the 3 years post-dose, all participants experienced at least 1 treatment-emergent AE (TEAE); of 709 events, 541 (76%) were mild, 137 (19%) were moderate, and 31 (4%) were severe. There were no serious AEs related to treatment [a serious AE of hepatocellular carcinoma (HCC) and a death were reported previously before Year 2 and determined to be unrelated to treatment]. A total of 38/54 (70%)

participants experienced 96 treatment-related TEAEs, of which 95% occurred before 6 months post-treatment. The most common AE was an increase in alanine transaminase (ALT), for which 9 (16.7%) participants received supportive care with reactive corticosteroids for a mean duration of 81.4 days (SD: 28.6; range: 51-130 days). No new deaths, no new HCC, and no late treatment-related ALT elevations or thromboembolic events were reported.

International consensus recommendations from 15 hematology specialists from Europe, Australia, Japan, Latin America, and North America state, "Based on current AAV hemophilia B gene therapy trial data, this therapy should be considered as a future treatment option in adults with severe hemophilia B". This recommendation was published prior to the FDA approval of etranacogene dezaparvovec and publication of pivotal trial results.

A 2020 guideline from the World Federation of Hemophilia (WFH) states, "Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies. This will require evaluation through long-term follow-up as part of clinical trials and registries."

The United Kingdom's National Institute for Health and Care Excellence (NICE) guidance on etranacogene dezaparvovec for the treatment of hemophilia B is under development and does not yet have an expected publication date.

Hemgenix has a WAC of $3.5 million and AWP of $4.2 million for a one-time infusion. Currently, people living with hemophilia B receive IV infusions of FIX that cost approximately $550,000-750,000 annually.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	96365: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour 96366: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
HCPCS Codes:	J1411: Injection, etranacogene dezaparvovec-drlb, per therapeutic dose
ICD10 codes:	D67: Hereditary factor IX deficiency
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	08/12/2024	New policy

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

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