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Etranacogene dezaparvovec-drlb

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Etranacogene dezaparvovec-drlb (Hemgenix) **may be considered medically necessary** if **ALL** the following criteria are met:

1. Individuals ≥ 18 years of age and assigned male at birth; AND
2. Individual has a confirmed diagnosis of severe or moderately severe hemophilia B (congenital Factor IX deficiency); AND
    a. Current use of Factor IX prophylaxis; or
    b. Current or historical life-threatening hemorrhage; or
    c. Repeated, serious spontaneous bleeding episodes; AND
3. Absence of Factor IX inhibitor, confirmed by Factor IX inhibitor titer testing; AND
4. Individual does **NOT** have any of the following:
    a. Significant liver disease (e.g., elevated alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase [ALT, AST, or ALP] greater than 2 times the upper limit of normal [ULN] or bilirubin greater than 1.5 times ULN);
    b. Active hepatitis B or C;
    c. Currently on antiviral therapy for hepatitis B or C;
    d. Serological evidence of human immunodeficiency virus (HIV-1 or HIV-2) with CD4 counts ≤ 200/mm^3;
    e. Prior gene therapy.

Etranacogene dezaparvovec-drlb (Hemgenix) **is considered experimental, investigational, and/or unproven** for all other indications.

Repeat treatment of etranacogene dezaparvovec-drlb (Hemgenix) **is considered experimental, investigational, and/or unproven**.

Policy Guidelines

Recommended Dose
The minimum recommended dose is 2 x 10^{13} genome copies (gc) per kg of body weight.

Dosing Limits
1 injection per lifetime.

Other Considerations
Etranacogene dezaparvovec-drlb was not studied in individuals assigned female at birth.

A baseline liver health assessment is recommended before starting treatment with etranacogene dezaparvovec-drlb. In cases of radiological liver abnormalities and/or sustained liver enzyme elevations, the prescriber is recommended to consider a consultation with a hepatologist to assess eligibility.

Where feasible, the individual should receive periodical monitoring for hepatotoxicity, hepatocellular carcinogenicity, Factor IX (FIX) activity, and FIX inhibitors.

Description

Hemophilia B

Hemophilia B is an inherited X-linked recessive congenital bleeding disorder that predominately affects males caused by mutations in the *F9* gene resulting in factor IX (FIX) being deficient, missing or functionally defective. (1 ,2) It is the second most common coagulation factor deficiency. It is estimated that number of prevalent cases of hemophilia B in the U.S. is between 6,300 and 7,600 as of 2018. (3) Reported prevalence rate of hemophilia B was estimated at 3.7 per 100,000 male population while the incidence rate was estimated at 5.3 per 100,000 male births, or 1 case per 19,283 live male births. Worldwide, there are approximately 33,000 people living with hemophilia B as of 2020. (4)

The severity of hemophilia has generally been defined by factor levels. (5) Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted. (6) Disease severity using factor level classifications is summarized in Table 1. Individuals with more severe hemophilia are more likely to have spontaneous bleeding, severe bleeding, and an earlier age of first bleeding episode, which can begin as early as birth. Those with severe disease, are at risk for potentially life-threatening bleeding episodes and debilitating long-term complications. (7) Individuals with severe hemophilia typically experience frequent, spontaneous bleeds (1 to 2 times per week) in their muscles or joints. (8) Repeated, spontaneous bleeding in the joints (hemarthrosis) results in joint inflammation and damage to joint cartilage and synovium leading to hemophilic arthropathy. (9) According to 1 study, hemophilic arthropathy was observed in >90% of those with severe hemophilia before the age of 30 years. (10) Severe hemophilia is almost exclusively a disease of males, although females can be affected in some rare cases (e.g., compound heterozygosity; skewed lyonization; X chromosome loss). In contrast, mild hemophilia has been reported in up to one-quarter of female carriers who are heterozygotes. Most commonly, hemophilia is inherited. However, sporadic disease (without a positive family history, presumed due to a new variant) is also common. Studies have demonstrated that sporadic causes account for as much as 43% of cases of severe hemophilia B. (11) In moderate and mild hemophilia B, approximately 30% are sporadic cases.

Table 1. Hemophilia Severity, Factor Levels and Symptoms (8)

Severity of Hemophilia[a]	Clotting Factor Levels	Symptoms
Mild	5% to 40% of normal	• Might bleed for a long time after surgery, dental extraction or a very bad injury

		• Rarely bleeds unless injured (rarely has spontaneous bleeding)
Moderate	1% to 5% of normal	• Might bleed for a long time after surgery, a bad injury, or dental work • Might bleed for o clear reason (occasional spontaneous bleeding)
Severe	Below 1% of normal	• Bleed often into the joints and sometimes the muscles • Can bleed for no obvious reason (spontaneous bleeding)

[a] Severity of hemophilia is measured in percentage of normal factor activity in the blood, or in number of international units (IU) per millilitre (mL) of whole blood. The normal range of clotting factor VIII or IX in the blood is 40% to 150%. People with factor activity levels of less than 40% are considered to have hemophilia. Some people's bleeding pattern does not match their baseline level. In these cases, the phenotypic severity (bleeding symptoms) is more important than the baseline level of factor in deciding upon treatment options.

Diagnosis

Hemophilia should be suspected in individuals who present with a history of easy bruising; "spontaneous" bleeding (i.e., bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues; excessive bleeding following trauma or surgery. Diagnosis is made by assessing the patient's personal and family history of bleeding and is confirmed through screening tests, including a complete blood count test and a blood coagulation tests, typically activated partial thromboplastin clotting time (aPTT) and a prothrombin time (PT) test. (12) Both tests measure the length of time it takes for blood to clot and are important in identifying the potential cause of bleeding; the aPTT test assesses the clotting ability of factors VIII, IX, XI and XII (and is thus relevant to hemophilia B) while the PT assay tests for factors I, II, V, VII and X. (13, 14) In the event of an abnormal aPTT result, diagnosis of hemophilia B is established by the following:

- Diagnosis of hemophilia B requires confirmation of a factor IX activity level below 40% of normal, or, in some circumstances where the factor IX activity level is ≥40%, a pathogenic variant in the *F9* gene. Newborns have a lower normal range of factor IX activity; the normal newborn range should be used as a reference when evaluating factor levels in newborns.

Genetic testing is recommended to identify the specific disease-causing gene mutation and evaluate the risk of inhibitor development. (12) Diagnosis is usually at a younger age among patients with the severe (≤2 years) or moderate (<5 to 6 years) form of the disorder compared with those with mild disease who are typically diagnosed later in life or in adulthood. (15)

Current Treatment

Factor replacement therapy is provided via one of two modalities: prophylaxis (regular replacement) or on demand (episodic). Prophylaxis is primary (before a bleeding event has occurred) or secondary (a bleeding event has occurred), and continuous or intermittent (e.g., for a few months at a time). Individuals with hemophilia, particularly those with severe

hemophilia, can be affected by development of inhibitors (antibodies that develop in response to exogenous administration of exogenous factors).

Several factor preparations are available for prophylaxis, some prepared from human plasma, some prepared using recombinant technology including some with modifications to extend the half-life of the therapy.

Regulatory Status
On November 22, 2022, etranacogene dezaparvovec-drlb (Hemgenix; CSL Behring) was approved by the U.S. Food and Drug Administration (FDA) 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

This medical policy was developed in 2022 and has been updated with a search of the PubMed database through July 14, 2023.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Etranacogene dezaparvovec-drlb for Congenital Hemophilia B
Clinical Context and Therapy Purpose

The purpose of etranacogene dezaparvovec-drlb in adults who have congenital hemophilia B is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- A novel mechanism of action or approach that may allow successful treatment of many individuals for whom other available treatments are not available or have failed or have yielded sub-optimal response.
- Reduced treatment complexity such as avoidance of repeated intravenous infusion or subcutaneous injections.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals who are adults with congenital hemophilia B who currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

Interventions
The therapy being considered is etranacogene dezaparvovec-drlb, an adeno-associated virus serotype 5 (AAV5) mediated gene therapy designed to deliver a copy of the gene encoding the Padua variant of human coagulation Factor IX (hFIX Padua).

Comparators
Life-long prophylaxis with exogenous factor replacement therapy is currently being used to manage individuals with congenital hemophilia B.

Outcomes
The general outcomes of interest are disease-specific survival, change in disease status, health status measures, quality of life, resource utilization, treatment-related mortality, and treatment-related morbidity. Relevant outcome measures in alphabetical order are summarized in Table 2.

Table 2. Health Outcome Measures Relevant to Hemophilia B

Outcome	Description	Relevance
Annual Bleeding Rate	• Applicants of other FDA approved products have relied on ABR to demonstrate clinical benefit. (16)	• Although it is a direct assessment of clinical benefit, it has limitations in that it is a relatively infrequent event inpatients on prophylactic factor regimens and the decision by a patient to treat a possible bleeding episode is usually somewhat subjective. (16)
Factor Activity Levels	• Factor activity levels is an objective endpoint.	• To consider factor activity level as a validated surrogate endpoint,

	• For gene therapies, functional and structural differences between the transgene and normal factor protein may present a challenge in understanding the relationship between numerically identical factor activity levels or levels that are within the normal range for the transgene protein and normal factor protein. (16)	clinical data to assess and quantitate the relationship between steady-state factor activity levels and bleeding outcomes in patients with severe hemophilia are critical. (16)
Haem-A-QoL	• Patient-reported outcome questionnaire validated for hemophilia; contains 6 domains: Consequences of Bleeding, Emotional Impact, Physical Functioning, Role Functioning, Treatment Concern, and Worry. (17) • Subscale and total scores range from 0 to 100. • 41 total items scored from 0 to 5 with higher scores indicating better health-related quality of life or less impairment for a particular subscale.	• The Haem-A-QoL has been validated for this population and trials. (18)
Joint Activity/Bleeding	• Joint examination using imaging measures such as x-rays, MRI, and ultrasound.	• No validated scales or instruments that quantify joint damage have been identified. • As per ISTH, target joints are major joints with ≥3 bleeding events within 6 months; bleeding in target joints is considered to be resolved if there are ≤2 bleeding events within 12 months. (5)
Resource Utilization	• Repeat intravenous infusions are burdensome and can result in non-adherence.	• It is estimated that more than 94% of direct healthcare costs for patients with severe hemophilia A are attributable to the cost of FVIII replacement therapy. (19, 20) Reduction in quantity as well

		as frequency of exogenous factor FVIII replacement is desirable.

ABR: annualized bleeding rate; FDA: U.S. Food and Drug Administration; FVIII: factor VIII; Haem-A-QoL: Haemophilia Quality of Life Questionnaire for Adults; ISTH: International Society on Thrombosis and Hemostasis; MRI: magnetic resonance imaging; QoL: quality of life.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The clinical development program is summarized in Table 3 and consists of 3 interventional studies (AMT-060-01, AMT-061-01 and AMT-061-021). All 3 interventional studies are single-arm, open-label trials. Of these, the first two studies, AMT-060-01 and AMT-061-01 were phase 1/2 studies and are not reviewed in detail. The key trial for etranacogene dezaparvovec-drlb is the Phase 3 Hope-B trial (AMT-061-021) that includes 54 participants and is reviewed in detail.

Table 3. Clinical Development Program for Etranacogene dezaparvovec-drlb

Study	NCT Number	Status	Study Dates	Objective	Sample Size	Follow-Up
CT-AMT-060-01	NCT02396342	Completed and published (21)	2015 to 2021	To evaluate the long-term safety and efficacy of AMT-060 comprising an AAV5 vector carrying a codon-optimized wild-type *F9* transgene	10	5 years
CT-AMT-061-01	NCT03489291	Ongoing and interim results published (22, 23)	2018 to 2023	To confirm the safety and preliminary efficacy endpoints of AMT-061 (etranacogene dezaparvovec-drlb), with a modified *F9* transgene	3	5 years

				encoding the naturally occurring hyperactive mutation, FIX-Padua, in place of wild-type *F9*		
CT-AMT-061-02 (HOPE-B)	NCT03569891	Ongoing	2018 to 2025	To evaluate the efficacy, and confirm the safety, of etranacogene dezaparvovec-drlb (as a progression of AMT-060).	54	5 years

AAV5: adeno-associated virus serotype 5; FIX-Padua: Padua variant of coagulation Factor IX; NCT: national clinical trial.

Nonrandomized Studies

Study characteristic and baseline patient characteristics and results are summarized in Table 4 and 5, respectively. The prospective, open-label, single-dose, single arm, multi-national study enrolled adult males aged 19 to 75 years, with severe or moderately severe Hemophilia B. Study design involved a prospective lead-in period of at least six months with the intent to receive standard of care routine factor IX prophylaxis. Study participants then received a single intravenous dose of etranacogene dezaparvovec-drlb and were then followed up monthly until month 12, and then at 6-month intervals until year 5. The study is on-going. For the efficacy evaluation for the U.S. Food and Drug Administration (FDA) approval, data up to 18 months post-treatment were used. (24) Of the 54 study participants, 53 completed at least 18 months of follow-up. One participant of 75 years of age with numerous cardiovascular and urologic risk factors died of urosepsis and cardiogenic shock at month 15 post-dose (at age 77 years) unrelated to treatment. Another participant received around 10% of the intended dose due to an infusion-related hypersensitivity reaction.

The primary efficacy outcome was a non-inferiority test of annualized bleeding rate (ABR) during months 7 to 18 after treatment compared with ABR during the lead-in period. All bleeding episodes, regardless of investigator assessment, were counted. Participants were allowed to continue prophylaxis during months 0 to 6. Results are summarized in Table 6. The ABR ratio (months 7 to 18 post-treatment/lead-in) was 0.46 [95% confidence interval [CI]: 0.26, 0.81] and meets the meets the success criterion where the upper bound of the CI is less than 1.8 demonstrating non-inferiority of ABR during months 7 to 18 compared to the lead-in period. Two study participants were not able to stop routine prophylaxis after treatment with etranacogene dezaparvovec-drlb. During months 7 to 18, an additional participant received prophylaxis from days 396 to 534 [approximately 20 weeks]. (25)

In AAV vector–based gene therapies such as etranacogene dezaparvovec-drlb, pre-existing anti-AAV neutralizing antibodies may impede transgene expression at desired therapeutic levels. In the clinical studies, an unvalidated clinical trial assay was utilized to assess pre-existing anti-

AAV5 neutralizing antibodies. There were 21 participants with a positive neutralizing antibodies to AAV5. These neutralizing antibodies titers were measured at baseline prior to infusion of the gene therapy product. The neutralizing antibodies titers were in the range of 1:8.5 to 3212. According to the FDA reviewer, overall, there is limited data for participants with positive NAb titers. One participant with the highest titer of 1:3212, failed treatment, continued on routine prophylaxis with multiple bleeding episodes. The FDA reviewers observed no clear correlation of positive neutralizing antibodies titers and efficacy. (24) Nine participants with higher ABRs post treatment compared to baseline included participants with and without neutralizing antibodies. FDA reviewers noted that four participants with positive neutralizing antibodies had much higher ABRs compared to those with negative neutralizing antibodies. According to the prescribing label, individuals who intend to receive treatment with Etranacogene dezaparvovec-drlb are encouraged to enroll in a study that evaluates the effect of pre-existing anti-AAV5 neutralizing antibodies on the risk of bleeding.

The most common adverse reactions (incidence ≥ 5%) were elevated alanine transaminase (ALT), headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, malaise, and elevated AST. One death was reported in due to cardiogenic shock and was deemed unrelated to treatment. (25) Nine participants were treated with corticosteroids for ALT elevation of either > 2 times upper limit of normal (ULN; n = 8) or >2 X baseline value (n = 1). Participants with ALT elevation had approximately 44% lower mean FIX activity at month 18 compared to those that did not have ALT elevation. Study participants (17% or 9/53) that were treated with corticosteroid for ALT elevations exhibited approximately 63% lower mean FIX activity at month 18 compared to those who did not receive corticosteroid coadministration. Participants were treated for 51-130 days. ALT elevation is likely the result of T-cell response toward capsid proteins and may cause the lower FIX activity as noted. All participant discontinued steroid use prior to week 26 and no other form of immunosuppression was used in this study. (24) As per the prescribing label, integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. As per the label, for individuals with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, and advanced age), regular (e.g., annual) liver ultrasound and alpha-fetoprotein testing should be performed following treatment. (25)

Table 4. Summary of Key Nonrandomized Trial

Study	**HOPE-B (24, 25)**
Study Type	Open-label, single-arm
Country	US, UK, EU
Dates	2018 to 2025
Participants	Inclusion: • Adult males with severe (FIX <1%) or moderately severe (FIX 1%-2%) hemophilia. • Received continuous FIX protein prophylaxis for ≥ 2 months. • >150 previous exposure days of treatment with FIX protein.

	Exclusion: • History of FIX inhibitors or positive FIX inhibitor test at screening. • Positive human immunodeficiency virus test at screening, not controlled with anti-viral therapy. • Active infection with hepatitis B or C virus at screening. • History of Hepatitis B or C exposure, currently controlled by antiviral therapy at the end of the lead-in phase. • Previous gene therapy treatment.
Treatment	• Screening period of approximately 4 weeks, followed by a ≥ 26-week lead-in phase with FIX prophylaxis, during which they were evaluated for bleeding events. • After the lead-in period, patients received a single dose of 2 x 10^{13} gc/kg of etranacogene dezaparvovec-drlb.
Follow-up	78 weeks (intended duration of study 5 years).

EU: European Union; FIX: factor IX; UK: United Kingdom; US: United States

Table 5. Summary of Baseline Demographics and Disease Characteristics

Patient Characteristics in (HOPE-B) (24, 25)	**N=54**
Age, mean (SD, min-max), years	41.5 (15.8, 19-75)
Race, n (%)	
White	40 (74.1)
Black	1 (1.9)
Asian	2 (3.7)
Other	6 (11.1)
Severity of hemophilia B at diagnosis, n (%)	
Severe (FIX <1%)	44 (81.5)
Moderately severe (FIX ≥1% and ≤2%)	10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	9 (16.7)
Prior hepatitis C infection, n (%)	31 (57.4)
Pre-screening FIX treatment (n, %)	
Extended half-life	31 (57.4)
Standard half-life	23 (42.6)
Detectable NAbs at baseline, n (%)	21 (38.8)
Participants with zero bleeds at lead-in, n (%)	14 (25.9)

FIX: factor IX; HIV: human immunodeficiency virus; Nabs: neutralizing antibodies; min-max: minimum-maximum; SD: standard deviation.

Table 6. Summary of Results

Outcomes (HOPE-B) (25)	**Pre-Study Period[a]**	**Post-Study Period (months 7 to 18[b] After Elivaldogene autotemcel treatment)**
Bleeding Related Outcome (Primary)		

All bleeds	136	96[c]
Follow-up time (person-year)	33	52
Mean adjusted ABR (95% CI)[d]	4.1 (3.2, 5.4)	1.9 (1.0, 3.4)
Subjects with bleeds	40 (74%)	20 (37%)
Subjects with zero bleeds	14 (26%)	34 (63%)
Observed spontaneous bleed count (proportion of total bleeds)[e]	50 (37%)	14 (26%)
Observed joint bleed count (proportion of total bleeds)[e]	77 (57%)	19 (35%)
Mean spontaneous ABR	1.52	0.44
Mean traumatic ABR	2.09	0.62
Number of bleeding episodes	136 (including 118 treated episodes)	54 (including 30 bleeding episodes)
Secondary Outcomes (24)		
FIX Activity (one-stage activated partial thromboplastin time-based assay), mean (±SD)	1.19 (0.39)	Month 6: 39.0 (18.7) Month 12: 41.5 (21.7) Month 18: 36.9 (21.4)
FIX Activity (chromogenic assay), mean (±SD), range	Not reported	Month 6: 38.95% ± 18.72, 8.2 to 97.1%) Month 12: 41.48% ± 21.71, 5.9 to 113.0%) Month 18: 36.90% ± 21.40, 4.5 to 122.9%)

ABR: Annual bleeding rate; CI: confidence interval; FIX: factor IX; SD: standard deviation.

[a] During the observational lead-in period subjects used their individualized approach to factor IX prophylaxis derived prior to enrollment in the study, rather than a standardized approach to factor IX prophylaxis. Not all subjects complied with their prescribed prophylaxis regimen during the lead-in period.

[b] Efficacy evaluation started from month 7 after etranacogene dezaparvovec-drlb treatment, to allow factor IX expression to reach a steady state.

[c] An ABR of 20 was imputed for the period when three subjects were on continuous prophylaxis.

[d] Non-inferiority comparison and mean ABR estimates were based on a repeated measures generalized estimating equations negative binomial regression model.

[e] For spontaneous and joint bleed counts, no imputation was done for the three subjects receiving continuous prophylaxis during months 7 to 18.

The purpose of the study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of evidence supporting the position statement. The limited representations of African Americans, Asians, and Hispanics makes it challenging to reach conclusions about the efficacy of etranacogene dezaparvovec-drlb in these racial groups. The FDA reviewer noted higher ABRs (during months 7 to18 compared with the lead-in period) among 14 non-white study participants compared to white study participants. (24) Because of the uncontrolled study design, limited sample size and relatively short follow-up, there is still

considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec-drlb compared with factor IX prophylaxis. It is not yet clear that the initial increase in factor IX levels will be maintained for decades. In addition, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. The small sample size creates uncertainty around the estimates of adverse events. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect and safety.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
HOPE-B (24, 25)	4. Enrolled populations do not reflect diversity.				1. Not sufficient duration for benefit. 2. Not sufficient duration for harms.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	HOPE-B (24, 25)
Allocation[a]	1. Participants not randomly allocated. 2. Allocation not concealed. 3. Allocation concealment unclear. 4. Inadequate control for selection bias.
Blinding[b]	1. Participants or study staff not blinded. 2. Outcome assessors not blinded. 3. Outcome assessed by treating physician. 4. Outcomes not assessed centrally.
Selective Reporting[c]	
Data Completeness[d]	

Power[e]	1. Power calculations not reported. 2. Power not calculated for primary outcome. 3. Power not based on clinically important difference.
Statistical[f]	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Etranacogene dezaparvovec-drlb for Congenital Hemophilia B

The evidence for use of etranacogene dezaparvovec-drlb (Hemgenix) for congenital hemophilia B consists of a single study. In the pivotal, open-label, phase III single-arm HOPE-B study, 54 study participants received a single intravenous infusion of etranacogene dezaparvovec-drlb. Of the 54 participants, 53 were included in the efficacy analysis. The estimated mean annualized bleeding rate during months 7 to 18 after treatment with etranacogene dezaparvovec-drlb was 1.9 bleeds/year (95% CI: 1.0 to 3.4) compared with an estimated mean annualized bleeding rate of 4.1 (95% CI: 3.2 to 5.4) during the lead-in period. The annualized bleeding rate ratio (months 7to 18 post-treatment / lead-in) was 0.46 (95% CI: 0.26 to 0.81) demonstrating non-inferiority of annualized bleeding rate during months 7 to 18 compared to the lead-in period. The ABR represents an appropriate clinical benefit endpoint for subjects with hemophilia B and the evidence of clinical benefit was demonstrated by reduction of bleeds in the efficacy evaluable period post treatment. Limitations include uncontrolled study design, limited sample size and relatively short follow-up. There is considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec-drlb compared with factor IX prophylaxis. It is not yet clear that the initial increase in factor IX levels will be maintained for decades. In addition, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma as limited sample size is prone to uncertainty around the estimates for adverse events. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect and safety.

Summary of Evidence

For individuals who are adults with congenital hemophilia B who currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes who receive etranacogene dezaparvovec-drlb (Hemgenix), the evidence includes a single prospective single-arm study. Relevant outcomes are disease-specific survival, change in disease status, quality of life, resource utilization, treatment-related mortality, and morbidity. The pivotal, open-label, phase III single-arm HOPE-B study enrolled 54 adult males with severe (factor IX <1%) or moderately severe (factor IX 1%-2%) hemophilia. Of the 54 participants, 53 were included in the efficacy analysis. The estimated mean annualized bleeding rate during months 7 to 18 after treatment with etranacogene dezaparvovec-drlb was 1.9 bleeds/year (95% confidence interval [CI]: 1.0 to 3.4) compared with an estimated mean annualized bleeding rate of 4.1 (95% CI: 3.2 to 5.4) during the lead-in period. The annualized bleeding rate (ABR) ratio (months 7 to 18 post-treatment / lead-in) was 0.46 (95% CI: 0.26 to 0.81) demonstrating non-inferiority of annualized bleeding rate during months 7 to 18 compared to the lead-in period. ABR represents an appropriate clinical benefit endpoint for subjects with hemophilia B and the evidence of clinical benefit was demonstrated by reduction of bleeds in the efficacy evaluable period post treatment. Limitations include uncontrolled study design, limited sample size and relatively short follow-up which is inadequate to assess durability of treatment effect and safety, especially those adverse events that are potentially rare or have delayed onset. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Institute for Clinical and Economic Review

On December 22, 2022, the Institute for Clinical and Economic Review (ICER) published a comparative clinical effectiveness and value of gene therapy for hemophilia B and an update on gene therapy for hemophilia A. The Report concluded that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec-drlb compared with factor IX prophylaxis. (26)

National Bleeding Disorders Foundations (27)

The National Bleeding Disorders Foundation's (formerly the National Hemophilia Foundation [NHF]) Medical and Scientific Advisory Council (MASAC) guidelines were developed before the approval of etranacogene dezaparvovec-drlb, and include the following recommendations:

- *MASAC Document 284 – MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System (April 11, 2024)*
  - Recombinant factor IX products are the recommended treatment of choice for patients with hemophilia B.
- *MASAC Document 267 – MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors (April 27, 2022)*
  - Prophylaxis should be initiated at an early age, ideally before age 3 years and prior to the second joint bleed; prophylaxis may be considered within the first six months of life to reduce occurrence of intracranial hemorrhage.
  - Prophylaxis should be individualized (by dose and or frequency adjustment) and sufficient to prevent all bleeds at all times.

- Options for prophylaxis include plasma-derived or recombinant standard half-life factor, extended half-life factor and non-factor replacement.

World Federation for Hemophilia

The World Federation for Hemophilia (WFH) guidelines were developed before the approval of etranacogene dezaparvovec-drlb. In these guidelines and recommendations, the preferred treatment strategy is pharmacologic treatment, and exogenous FIX replacement by IV injection of recombinant FIX or human plasma-derived FIX concentrates is the recommended treatment of choice for patients with hemophilia B. (12)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J1411, J3490, J3590

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/15/2024	Document updated with literature review. The following change was made to Coverage: Removed "as defined by a plasma Factor IX (FIX) activity level ≤ 2%" from criteria. Added/updated references 7-11, 14, 25 and 27; others removed.
01/01/2024	Document updated with literature review. The following changes were made to Coverage: 1) Criteria revised to include "and assigned male at birth"; and 2) Criteria for diagnosis revised to include "severe or moderately severe hemophilia B (congenital Factor IX deficiency) as defined by a plasma Factor IX (FIX) activity level ≤ 2%". Added references 1-14, 16-21, 23, 25; some revised; others removed.
04/01/2023	New medical document. Etranacogene dezaparvovec-drlb (Hemgenix) may be considered medically necessary if ALL of the criteria noted in coverage are met. Etranacogene dezaparvovec-drlb (Hemgenix) is considered experimental, investigational, and/or unproven for all other indications. Repeat treatment of Etranacogene dezaparvovec-drlb (Hemgenix) is considered experimental, investigational, and/or unproven.