Medical Policy
Gene Therapies for Hemophilia B

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Information Pertaining to All Policies
- Policy History
- References

Policy Number: 168
BCBSA Reference Number: N/A
NCD/LCD: N/A

Related Policies
Prior Authorization Request Form for Hemgenix® (Etranacogene dezaparvovec), #169

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Prior Authorization Request Form: Hemgenix® (Etranacogene dezaparvovec)
*This form must be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.

Prior Authorization Request Form for Hemgenix® (Etranacogene dezaparvovec), #169

Entranacogene dezaparvovec (Hemgenix®)

Entranacogene dezaparvovec (Hemgenix) may be considered MEDICALLY NECESSARY and may be covered for individuals with Hemophilia B with congenital Factor IX deficiency when ALL the following criteria are met:

1. Individual is 18 years of age or older; AND
2. Individual has severe or moderately severe hemophilia B as defined by a plasma Factor IX (FIX) activity level ≤ 2%, as documented by written physician attestation AND historical records OR chart notes; AND
3. Must currently be on factor IX therapy with greater than 150 prior exposure days to treatment; AND
4. Individual meets one of the following:
   a. Current or historical life-threatening hemorrhage OR
   b. Repeated, serious spontaneous bleeding episodes; AND
5. Individual does not have a history of FIX inhibitors or a positive screen results of ≥ 0.6 Bethesda Units (BU) using the Nijmegen-Bethesda assay; AND
6. Individual has received a liver health assessment including enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] AND a hepatic ultrasound and elastography; AND
7. Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia B; **AND**
8. Individual does not have a history of receiving gene therapy or under consideration for treatment for another gene therapy for hemophilia B; **AND**
9. Individual is HIV negative or has a controlled HIV infection; **AND**
10. Individual does not have an active hepatitis B and/or hepatitis C infection.

**Note:** The safety and effectiveness of repeat administration of entranacogene dezaparvovec (Hemgenix) has not been evaluated. Therefore, coverage will be limited to once per lifetime. The use of entranacogene dezaparvovec (Hemgenix) that does not meet the criteria as indicated in this policy is considered **EXPERIMENTAL/INVESTIGATIONAL** and therefore non-covered because the safety and/or effectiveness of this service cannot be established by the available published peer-reviewed literature.

Betibeglogene autotemcel is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment of betibeglogene autotemcel is considered **INVESTIGATIONAL**.

Betibeglogene autotemcel is considered **INVESTIGATIONAL** for all other indications.

**Policy Guidelines**

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

**Dosing Limits:** 1 injection per lifetime

**Other Considerations:**
Where feasible, the individual should receive periodical monitoring for hepatotoxicity, hepatocellular carcinogenicity, FIX activity, and FIX inhibitors.

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 for entranacogene dezaparvovec-drlb.

**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| Commercial Managed Care (HMO and POS) | *Prior authorization is required. |
| Commercial PPO and Indemnity          | *Prior authorization is required. |
| Medicare HMO Blue℠                    | *Prior authorization is required. |
| Medicare PPO Blue℠                    | *Prior authorization is required. |

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.
The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1411</td>
<td>Injection, etranacogene dezaparvovec-drlb, per therapeutic dose</td>
</tr>
</tbody>
</table>

**ICD-10 Procedure Codes**

<table>
<thead>
<tr>
<th>ICD-10 PCS Procedure Codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>XW033F3</td>
<td>Introduction of Other New Technology Therapeutic Substance into Peripheral Vein, Percutaneous Approach, New Technology Group 3</td>
</tr>
</tbody>
</table>

**SUMMARY**

**Background**

**Hemophilia B**

Hemophilia B is a recessive X-linked congenital bleeding disorder, caused by mutations in the F9 gene resulting in FIX being deficient, missing or functionally defective.\(^1\)\(^2\) It is the second most common coagulation factor deficiency. Because it is a X-linked recessive inheritance, hemophilia predominately affect males but females can have FIX deficiency and female cases of hemophilia B, while less common than male cases, have been noted in the literature. A study of data from the 139 US HTCs (N=27,232 patients receiving care from 2012 to 2020) found that 8.5% of patients treated for hemophilia B were female (vs 91.5% males); females accounted for close to a quarter (23.7%) of mild hemophilia B cases but had very low rates (<1%) of moderate or severe disease.\(^3\) More than 50% of all patients with hemophilia B have no known family history of the disease. Deficiency or absence of FIX results in impaired hemostasis, prolonged bleeding, and rebleeding. Joint disease and hemarthrosis are the leading complications.\(^4\) Spontaneous and recurring hemarthroses cause progressive joint damage, gradually resulting in end-stage hemophilic arthropathy.\(^5\) Arthritis, a common type of arthropathy, is highly prevalent in patients with hemophilia B, especially those with severe disease.\(^1\)\(^4\)\(^6\).

It is estimated that number of prevalent cases of hemophilia B in the US is between 6,300 and 7,600 as of 2018.\(^7\) 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.\(^8\)

The severity of hemophilia B has generally been defined by factor levels.\(^9\) Severity based on factor levels does not perfectly correlate with any individual’s clinical severity, but no other classification system is widely accepted.\(^10\) Hemophilia B may be characterized as severe, moderate, or mild based on factor level correlating with the disease pattern\(^4\) and summarized in Table 1.

### Table 1. Hemophilia B Severity, FIX Activity Levels and Symptoms\(^4\)\(^11\)\(^9\).

<table>
<thead>
<tr>
<th>Severity</th>
<th>FIX Activity</th>
<th>Symptoms</th>
<th>Usual Age at Diagnosis</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥ 5% to 40% of normal</td>
<td>- Rare spontaneous bleeding</td>
<td>Later in life, depending on hemostatic challenges</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Excessive and/or prolonged bleeding after major injuries, surgery or tooth extractions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- May not be diagnosed until an injury, surgery or tooth extraction that results in prolonged bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
First episode may only occur in adulthood

<table>
<thead>
<tr>
<th>Severity</th>
<th>Percentage of normal</th>
<th>Bleeding Characteristics</th>
<th>Age</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>1 to 5%</td>
<td>Occasional spontaneous bleedings, Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions</td>
<td>&lt;5-6 years</td>
<td>41%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Have at least monthly bleeds, most frequently in joints without preceding trauma</td>
<td>≤2 years</td>
<td>30%</td>
</tr>
</tbody>
</table>

**FIX: factor IX.**

**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. 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. In the event of an abnormal aPTT result, diagnosis of hemophilia B is established by a one-stage aPTT based FIX assay, which measures the patient’s FIX activity level and thus confirms whether the patient has FIX deficiency and how severe it is. Following the FIX assay, genetic testing is recommended to identify the specific disease-causing gene mutation and evaluate the risk of inhibitor development. Diagnosis is usually at a younger age among patients with the severe (≤2 years) or moderate (<5-6 years) form of the disorder compared with those with mild disease who are typically diagnosed later in life or in adulthood.

**Current Treatment**

FIX replacement therapy is provided via one of two modalities: prophylaxis (regular replacement) or on demand (episodic). Primary prophylaxis consists of regular and continuous FIX replacement therapy in the absence of documented joint disease and is initiated before the age of 3 years and the second clinically evident joint bleed. In secondary prophylaxis, regular and continuous infusions are started after the patient has two or more joint bleeds before the onset of joint disease, typically at or after the age of 3 years. Tertiary prophylaxis is initiated after the onset of documented joint disease, usually in adulthood. As per the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia, the standard of care for patients with severe hemophilia B is FIX prophylaxis to prevent bleeding, with initiation early in life before the age of 3 years to prevent musculoskeletal complications from recurrent joint and muscle bleeds. The goal of prophylaxis has been to maintain trough levels of circulating FIX at >1% of normal at all times to prevent spontaneous bleeds; however, the evidence has increasingly shown that trough levels at 1 to 3% of normal are insufficient to prevent bleeds completely in people with hemophilia B, the result being that some clinicians prefer >3 to 5% as the target trough range. FIX prophylaxis requires regular and frequent IV FIX infusions and regular venous access. The most serious complication of replacement therapy is inhibitor development. FIX inhibitors are alloergic antibodies to FIX that reduce or eliminate the activity of FIX. Approximately 1% to 3% of patients with hemophilia B develop inhibitors following exposure to FIX replacement therapy. Among patients with severe hemophilia B, the percentage has, however, been reported to be as high as 9%. 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. Recombinant FIX preparations are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation, but these are not first-line therapy. All approved products are approved for the indications, control, and prevention of bleeding episodes and perioperative management. Rixubis, Alprolix, and Idelvion are approved for the additional indication of routine prophylaxis. The goal of maintaining FIX activity levels of at least 1% (routine prophylaxis) requires regularly scheduled FIX
infusions. For routine prophylaxis, the labeled dosing frequency is twice a week for Rixubis, once every 7 to 10 days for Alprolix, and once every 7 days for Idelvion. The National Hemophilia Foundation (NHF) guidelines recommend recombinant over plasma-derived FIX concentrates as the preferred option. 15

Summary of Evidence

The evidence for use of etranacogene dezaparvovec-drlb for 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 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. 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>NCT No</th>
<th>Status</th>
<th>Study Dates</th>
<th>Objective</th>
<th>Sample Size</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-AMT-060-01</td>
<td>NCT02396342</td>
<td>Completed and published</td>
<td>2015 to 2021</td>
<td>To evaluate the long-term safety and efficacy of AMT-060 comprising an AAV5 vector carrying a codon-optimized wild-type F9 transgene</td>
<td>10</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT-AMT-061-01</td>
<td>NCT03489291</td>
<td>Ongoing interim results</td>
<td>2018 to 2023</td>
<td>To confirm the safety and preliminary efficacy endpoints of AMT-061 (etranacogene dezaparvovec-drlb), with a modified F9 transgene encoding the naturally occurring hyperactive mutation, FIX-Padua, in place of wild-type F9</td>
<td>3</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>published</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT-AMT-061-02</td>
<td>NCT03569891</td>
<td>Ongoing</td>
<td>2018 to 2025</td>
<td>To evaluate the efficacy, and confirm the safety, of etranacogene dezaparvovec-drlb (as a progression of AMT-060).</td>
<td>54</td>
<td>5 years</td>
</tr>
<tr>
<td>(HOPE-B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
allo-HSCT: allogenic hematopoietic stem cell transplant; CALD: cerebral adrenoleukodystrophy; eli-cel: elivaldogene autotemcel; FIX: factor IX.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/9/2023</td>
<td>Policy revised. Updated criteria for medical necessity to include: 1) physician attestation and historical records or chart notes to establish severity of hemophilia B; 2) greater than 150 prior exposure days to treatment for current factor therapy criteria. Effective 8/9/2023.</td>
</tr>
<tr>
<td>5/2/2023</td>
<td>Updated Criteria for medical necessity – Age, assigned sex at birth, disease severity, FIX therapy requirements, exclusion criteria, baseline test requirements</td>
</tr>
<tr>
<td>4/13/2023</td>
<td>Removed - Baseline anti-AAV5 antibodies &gt; 1:678 in from criteria #5 list of exclusions. It is not an FDA requirement, and is not present in the HEMGENIX product label</td>
</tr>
<tr>
<td>04/03/2023</td>
<td>New medical policy describing medically necessary and investigational indications. Policy created with literature review.</td>
</tr>
</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


