Molina Clinical Policy
Hemgenix (etranacogene dezaparvovec-drlb): Policy No. 429

Last Approval: 12/11/2024
Next Review Due By: December 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses the use of Hemgenix for the treatment of Hemophilia B.

Hemgenix is indicated for the treatment of severe hemophilia B (congenital factor IX deficiency) in adult patients who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. Candidates for Hemgenix should not have a history of factor IX inhibitors or detectable antibodies to AAV5.

Hemophilia encompasses a group of bleeding disorders caused by deficiency of a coagulation factor. Deficiency of factor VIII causes hemophilia A, deficiency of factor IX causes hemophilia B, and deficiency of factor XI causes hemophilia C. Hemophilia is most often inherited, but rare cases are acquired later in life. Hemophilia A and B are X-linked recessive bleeding disorders, while Hemophilia C follows an autosomal recessive inheritance pattern. The genetic mutation is found on chromosome 4. In the United States, approximately 30,000 to 33,000 people have hemophilia, with Hemophilia A being four times as common as hemophilia B. Hemophilia A has an incidence of one in 5,000 male live births compared to one in 30,000 for hemophilia B (CDC 2022). Hemophilia B represents an estimated 15% of hemophilia patients (FDA 2022). Hemarthrosis, the hallmark of severe hemophilia, is the major cause of serious bleeding events, disability, and reduced quality of life in patients with factor VIII or factor IX deficiency. Repeated hemarthrosis frequently results in hemophilic arthropathy, which is characterized by cartilage and bone degradation, bone remodeling, and progressive loss of function.

Hemophilia B (Christmas Disease) a deficiency in Factor IX clotting activity, results in spontaneous bleeding in the absence of trauma and delayed or recurrent bleeding prior to complete wound healing (Shah et al. 2022). Factor levels (an individual's percentage of factor IX) have traditionally been used to assess the severity of hemophilia B. Although severity based on factor levels does not perfectly correlate with clinical severity in any individual, no other classification system is widely accepted. Severe disease is defined by factor levels less than 1% of normal, according to factor level classifications (Refer to 'Supplemental Information' section for additional information on severity). In severe disease, recurrent bleeds typically result in arthropathy, joint contractures, and pseudotumors. Severe disease leads to chronic pain, disability, and a diminished quality of life. The current standard of care is Factor IX replacement therapy, with moderate to severe hemophilia B patients receiving prophylactic infusions of Factor IX. Gene therapy for the treatment of hemophilia B aims to alter the clinical phenotype of hemophilia to a milder form or cure by increasing endogenous coagulation factor levels via the transfer of a functional gene encoding the respective deficient coagulation factor and subsequent transgene expression. In the absence of longer-term data on efficacy and durability of gene therapy the probability of a cure or permanent physiologic recovery remain unknown.

Hemgenix (etranacogene dezaparvovec-drlb, or etrana-dez; formerly AMT-061) is a gene therapy for hemophilia B. Hemgenix adds a functional copy of the factor IX gene back to a person with hemophilia B via a viral vector. The viral vector is an adeno-associated virus, serotype 5 (AAV5). The factor IX gene delivered by the viral vector is modified to be more active than the typical factor IX gene. Its enhanced activity is secondary to a variation in the gene's code. This code variation is called the Padua variant. The expression of this functionally enhanced factor IX gene is driven by a liver-selective promoter. A one-time infusion of Hemgenix results in production of an

active factor IX clotting factor. Patients undergoing gene therapy may still require on-demand factor therapy, which should be accessible in cases such as trauma, surgery, and spontaneous bleeding.

FDA approval in November 2022 was based on an 18-month interim analysis of data from the HOPE-B trial, a Phase 3, open-label, single-dose, multi-center, multinational trial. A total of 54 of the 67 enrolled adult males with severe or moderately severe hemophilia B were dosed with etrana-dez and were included in the analysis (NCT03569891). Fifty-two (96%) of 54 participants expressed endogenous factor IX and remained free of factor IX prophylaxis at month 24

Long-term durability of clinical benefit and safety of gene therapy for hemophilia remains unknown. Potential safety issues include genotoxicity, protein overexpression and immunotoxicity. Other concerns are that insertional mutagenesis could lead to infertility or, indirectly, to birth defects, and horizontal and vertical transmission (Batty and Lillicrap 2021) of exogenous gene material. There are also uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma due to the integration of AAV vector DNA into the genome (ICER 2022). Longer follow-up is required to fully assess the benefits and potential risks of these treatments.

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Hemgenix (extranacogene dezoparvovec-drlb) for the treatment of hemophilia B may be considered medically necessary when **ALL** the following criteria are met with relevant documentation:

1. A diagnosis of hemophilia B in an adult (age 18 and older) male
2. Severe hemophilia B defined by Factor IX baseline residual level less than or equal to 1 IU/dL
3. Member is on Factor IX prophylaxis with a minimum of 150 exposure days to factor replacement
4. Member has not received, or is being considered for other gene therapy, or investigational cellular therapy for hemophilia
5. No presence or history of Factor IX inhibitors (Factor IX inhibitor titer test results required).
   NOTE: The definition of a positive inhibitor is a Bethesda titer of ≥0.3 BU for Factor IX (World Federation of Hemophilia Guidelines, 3rd edition)
6. HIV status is ONE of the following:
   a. Member is HIV negative documented by lab test within the past 3 months
   b. HIV positive AND well-controlled on antiretroviral therapy
7. Hepatitis B and C status is ONE of the following:
   a. Member does NOT have an active infection with hepatitis B or C virus documented by the following lab tests within the past 3 months (BOTH of the following):
      i. Negative hepatitis B surface antigen
      ii. Negative hepatitis C virus (HCV) antibody, OR HCV antibody is positive AND HCV RNA is negative
   b. For members with a history of hepatitis B or C exposure: Member is NOT currently using antiviral therapy for hepatitis B or C
8. Member has had a liver evaluation within the last 30 days and the following lab values are < 3 times the upper limit of normal:
   a. Alanine aminotransferase and Aspartate aminotransferase
   b. Total bilirubin and alkaline phosphatase

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling at this time.

The following are considered **exclusions** based on insufficient evidence:

1. Prior treatment with Hemgenix or other gene therapy for hemophilia, or being considered for treatment with other gene therapy
2. Current participation, or anticipated participation in any interventional clinical trial involving drugs or devices within one year of Hemgenix therapy
3. Positive Factor IX inhibitor test, or history of Factor IX inhibitors
4. Positive for HIV and not controlled with anti-viral therapy
5. Hepatic impairment or disease, defined by ANY of the following:
    - Advanced hepatic impairment (e.g., cirrhosis, advanced liver fibrosis)
    - Active, uncontrolled Hepatitis B or C
    - Alanine transaminase at least 3 times the upper limit of normal
    - Alkaline phosphatase at least 3 times the upper limit of normal
    - Bilirubin at least 3 times the upper limit of normal

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indications other than those listed above
2. Any criterion listed above that is not met by the member or that is submitted without the required supporting documentation

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by a board-certified hematologist in coordination with a Hemophilia Treatment Center for administration.

AGE RESTRICTIONS: Age ≥18 years at the time of infusion

GENDER RESTRICTIONS: Male

DOSING CONSIDERATIONS: Recommended dose is 2 x 10^{13} genome copies (gc) per kg of body weight as a one-time IV infusion.

MONITORING PARAMETERS: Member should be monitored according to FDA-approved labeling and best practice.

QUANTITY LIMITATIONS: ONE (1) treatment course of Hemgenix per lifetime. Additional infusions will not be authorized.

ADMINISTRATION: Hemgenix is considered a provider-administered therapy in a Hemophilia Treatment Center by a physician(s) with experience in the treatment of patients with hemophilia B.

CONTINUATION OF THERAPY: Not applicable as this is a one-time therapy. Reauthorization requests or requests for additional therapy beyond a single dose are considered experimental and will not be authorized.

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Repeat administration of is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Hemgenix. The evidence is insufficient to determine the effects on net health outcomes.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The Biologics License Application (BLA) for etrana-dez is supported by results from the phase 2 AMT-061-01 (NCT03489291) and the pivotal HOPE-B trial (NCT03569891). Both are single-arm trials that included adult males

with moderately severe to severe hemophilia B. The annualized bleeding rate (ABR) at 52 weeks was assessed as a primary outcome in the HOPE-B trial, while factor IX activity was considered a primary outcome for the Phase 2b trial. The patients in these two trials received a single dose of etrana-dez 2 x 10^{13} gc/kg.

Pivotal Phase 3 Trial
The effectiveness was determined by reductions in the ABR of adult males. The trial reported increased Factor IX activity levels and a decreased need for routine Factor IX replacement prophylaxis. The annualized bleeding rate for all bleeds after stable factor IX expression, assessed at 18 months, was reduced by 54%. The vast majority of patients treated with Hemgenix (96% of patients) discontinued use of prophylaxis and remained free of previous continuous routine prophylaxis therapy.

Inclusion criteria were males, at least 18 years old, with a diagnosis of severe or moderately severe congenital hemophilia B, currently on factor IX prophylaxis and exposure to Factor IX protein for at least 150 days. Key exclusion criteria included a history of Factor IX inhibitors or a positive Factor IX inhibitor test at screening, select liver screening laboratory test values over 2 times the upper limit of normal or history of hepatitis B or C or active infection (given the risk of potential hepatotoxicity), a positive HIV test that is not controlled with antiviral therapy, and previous gene therapy treatment.

HOPE-B (Health Outcomes with Padua gene: Evaluation in Hemophilia B; NCT03569891). The pivotal Phase 3 HOPE-B trial is an **ongoing,** single-arm, open-label multinational study to assess the safety and effectiveness of Hemgenix (n=54). Adult males with moderately severe to severe hemophilia B requiring prophylactic Factor IX replacement therapy were enrolled in a prospective, ≥ 6 month observational period during which they continued to use their current standard of care therapy to establish an ABR baseline. After a 6-month lead-in, 54 patients received a single intravenous infusion of Hemgenix at a dose of 2 x 10^{13} gc/kg and 53 participants completed at least 18 months of follow-up. The primary outcome was ABR at 52 weeks.

Annualized Bleeding Rates

Bleed Type	**Relative Risk Reduction*** **Comparing ABR following gene therapy to the ABR for the same participants on factor prophylaxis prior to gene therapy*
Treated Joint Bleeds	80%
Treated Bleeds	77%
All Bleeds	64%

All reductions were clinically and statistically significant. Patients treated with etrana-dez had an 80% reduction in treated joint bleeds and similar reductions in other bleeds when compared with their bleeding rates on factor prophylaxis. The trial met its primary endpoint of reduction in ABR post-treatment compared with baseline Factor IX prophylactic therapy. The 52-week adjusted ABR for all bleeds was reduced by 64% (P = 0.0002) from 4.19 during the 6-month lead-in period to 1.51 during months 7 to 18.

- The mean adjusted ABR for all bleeds was reduced by 54% compared to the six-month lead-in period on Factor IX prophylactic replacement therapy (4.1 to 1.9).
- Results indicate that Hemgenix produced mean Factor IX activity of 39.0 IU/dL (range: 8.2-97.1) at 6 months, 41.5 (range 5.9-113) at 12 months, and 36.9 IU/dL (range: 4.5-122.9) at 18 months post-treatment. *While none of the responders resumed factor prophylaxis during the trial's 18-month duration, the long-term outcomes are unknown. At 18 months, the levels were marginally lower than at 6 and 12 months. It remains to be established if the lowering trend persists over time or if the levels of factor expression remain steady after numerous years of follow-up.*
- It should also be noted that at 6 months after gene therapy, factor levels ranged from 8.2 to 97.1 IU/dL, demonstrating a wide range of clinical response and variability.
- In addition, 94% of study participants (51 out of 54) who received Hemgenix discontinued use of prophylaxis and remained free of previous continuous routine prophylaxis therapy (Prescribing information, 2022)). Two participants were unable to stop routine prophylaxis after gene therapy treatment: one had high antibody titers to the adeno-associated virus vector at baseline and the second only received 10% of the target dose. The third participant stopped prophylaxis at 6 months per study protocol but received it again during days 396 to 534.
- Preexisting AAV5 NAbs were not used as an exclusion criterion. Benefits were reported regardless of the

preexisting antibodies which suggests that nearly all individuals with hemophilia B may benefit from treatment.

Hemgenix was generally well-tolerated with over 80% of adverse events (AEs) considered mild. No serious AEs were reported in a safety analysis combining data from the 2 clinical studies (n=3 and n=54). The most common AEs were alanine aminotransferase (ALT) elevations (42%), aspartate aminotransferase (AST) elevations (42%), blood creatine kinase elevations (42%), infusion-related reactions (33%), headache (18%), flu-like symptoms (14%), fatigue (12%) and malaise (12%). No inhibitors to Factor IX were reported.

- One patient had a significant adverse event related to hepatocellular cancer. However, according to independent molecular characterization and vector integration study of the tumor and surrounding tissue the hepatocellular carcinoma was not associated with Hemgenix therapy.
- According to the FDA prescribing information: *"the integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development."* While AAV is a non-integrating vector, it may integrate in small amounts into the nuclear genome; the long-term clinical implications and risk of cancer are unknown.

Follow-up publication of the 18 month data cut in March 2023 (Pipe et al. 2023) noted etranacogene gene therapy was superior to prophylactic factor IX therapy with respect to annualized bleeding rate (using the lead in period as a comparator). Limitations of the study include a relatively small sample size, as well as the inability to confirm the long-term durability of this single dose. It should also be noted that not all individuals were able to stop prophylaxis after treatment and one out of the 54 participants resumed prophylaxis use after stopping for approximately 6 months, suggesting there may be variable efficacy and a possible waning effect of the treatment. Additional long-term data is needed to establish the durability of Hemgenix in reducing bleeding and long-term complications, particularly as compared to standard of care factor replacement therapy (including Factor IX preparations with longer half-lives).

In 2024 Coppens et al., reported an additional 6 months of follow-up data. This new data, 24 months post gene therapy, demonstrated continued factor IX activity and sustained ABR reduction. There were no new safety concerns and there was no difference in efficacy between those with neutralizing antibody and those without. Participant data with neutralizing antibody were available for titers up to 1:678. There was one participant with a neutralizing antibody titer at 1:3212 who did not express factor IX.

Itzler et al., (2024) reported that several domains in the health related quality of life scale were significantly improved. Those domains were Treatment, Feelings, Work/School and Future.

HOPE-B is expected to conclude in March 2025.

Post-Marketing Study
With the BLA approval, the FDA required a post-marketing study (NCT06003387) to assess the correlation between the serious risk of bleeding associated with the failure of the expected pharmacological action of Hemgenix and pre-existing anti-AAV5 NAbs to the capsid of Hemgenix using a validated assay. The study will include at least 35 hemophilia B patients treated with Hemgenix, with at least 10 having pre-treatment anti-AAV5 NAbs titers of 1:1400 or higher. The trial will assess ABR before and after therapy. The study is expected to be completed by December 31, 2028.

National and Specialty Organizations

World Federation of Hemophilia (WFH)
Guidelines for the Management of Hemophilia 2020, 3rd edition
The guidelines strongly advise individuals with a severe phenotype of both hemophilia A and hemophilia B to be on prophylaxis adequate to avoid all bleeding. Long-term prophylaxis is recommended as the standard of care, particularly in children, to prevent bleeding, hemarthrosis, and to improve quality of life. The prophylactic regimen should, whenever possible, be individualized for each patient based on bleeding phenotype, unique pharmacokinetics, and joint status. The guidelines do not specify a preference for recombinant over plasma-derived clotting factor concentrates and indicate that the selection between these product types should be determined based on availability, cost, and patient preferences.

For pediatric patients with severe hemophilia, WFH recommends initiating prophylaxis with clotting factor early (before age 3 and before the onset of joint disease). The dosing and interval for clotting factor prophylaxis (either standard or extended half-life) should be adequate to prevent spontaneous and breakthrough bleeding, as well as

hemarthrosis. The WFH recommends escalation of prophylactic dose and orthopedic interventions in the event of a breakthrough bleed while on a prophylactic regimen.

The guidelines address gene therapy in general, noting that '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 current 2020 guidelines include no specific recommendations for etrana-dez.

A Gene Therapy Registry is being established to compile long-term data on the safety and efficacy of hemophilia patients treated with gene therapies to gain understanding and evidence about durability and variability of therapies (Konkle et al. 2021).

Institute for Clinical and Economic Review (ICER)
ICER published the Final Evidence Report assessing the comparative clinical effectiveness and value of etrana-dez (Hemgenix, CSL Behring) for hemophilia B (December 22, 2022).

ICER acknowledged from the patients' perspective that treatment with etrana-dez resulted in a significant reduction in ABRs, ranging between 64% for all bleeds to 80% for treated joint bleeds, as reported from the Phase 3 HOPE-B trial, in addition to alleviating the pain and minimizing potential disability from bleeding events. The reduction in burden of therapy from weekly or more frequent intravenous Factor IX injection was also highlighted as a significant important benefit, with 96% of the participants in the HOPE-B trial discontinuing FIX prophylaxis. Of note, 100% of the 52 patients with successful transduction during the initial 18 months of treatment were free from continuous FIX prophylaxis; none of the patients were required to resume factor prophylaxis.

The report states that while the results are encouraging, it is not yet evident if the initial elevation in factor IX levels will be sustained for decades. There is still considerable uncertainty regarding the long-term net benefits of etrana-dez in comparison to factor IX prophylaxis due to the uncontrolled study design, small number of patients studied, and relatively brief follow-up. Particularly, the long-term effects of the therapy on liver function and the risk of hepatocellular carcinoma are unknown. ICER concluded 'moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis.

SUPPLEMENTAL INFORMATION

Hemophilia B disease severity is classified as mild, moderate, or severe based on the plasma concentration of Factor IX (normal activity level 50%-150%):

- **Mild** is defined as factor IX activity > 5%-40% (> 0.05-0.4 units/mL), is usually diagnosed later in life, and is characterized by prolonged bleeding following major trauma or surgery.
- **Moderate** is defined as factor IX activity ≥1%-5% (0.01-0.05 units/mL), is usually diagnosed between age 5 and 6 years, and is characterized by bleeding following minor trauma but may present with spontaneous bleeding.
- **Severe** is defined as factor IX activity < 1% (< 0.01 units/mL), is usually diagnosed in the first 2 years of life and may present with spontaneous mild or life-threatening bleeding.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review. Edited overview for readability and updated medical summary and references. No changes to criteria.
12/13/2023	Annual review. Updated Overview, Summary of Evidence, and References.
01/04/2023	New policy. IRO Peer Review. 12/30/2022. Policy was reviewed by practicing physician board-certified in Oncology/Hematology.

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