Medical Policy

BlueCross BlueShield Kansas
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Title: Hemophilia B Gene Therapy Medical Drug Criteria Program Summary

Professional / Institutional
Original Effective Date: May 5, 2023
Latest Review Date: October 2, 2023
Current Effective Date: May 5, 2023

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FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Hemgenix® (etranacogene dezaparvovec-drlb) Suspension for intravenous infusion	• Treatment of adults with Hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy • Treatment of adults with Hemophilia B (congenital Factor IX deficiency) who have current or historical life-threatening hemorrhage • Treatment of adults with Hemophilia B (congenital Factor IX deficiency) who have repeated, serious spontaneous bleeding episodes		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Hemophilia B	Hemophilia B, also called Factor IX (FIX) deficiency or Christmas disease, is a genetic disorder caused by missing or defective Factor IX, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation.(2) The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(3) • Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia • Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding • Episodic CFC replacement should not be considered a long- term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications • Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation) • The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future • Gene therapy should make it possible or 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 • Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities The MASAC suggests the number of doses required for provision of home therapy varies greatly and is dependent

	upon the type of hemophilia (FVIII, FIX), the level of severity (severe, moderate, mild), the presence of an inhibitor, the prescribed regimen (on-demand, prophylaxis, immune tolerance), the number of bleeding episodes experienced regardless of the prescribed regimen, individual pharmacokinetics, the products utilized, and the level of physical activity. For patients on prophylaxis, a minimum of one major dose and two minor doses should be available in addition to the prophylactic doses utilized monthly. For patients with severe or moderate hemophilia treated on-demand, the number of doses required to be available at home may be based upon historical bleeding patterns, with at least one major and two minor doses added to assure a level of safety.(4) A major dose is defined as a correction of clotting factor that achieves a level of 60-100+% clotting factor activity that is utilized to treat a bleeding episode that is expected to require a higher hemostatic level such as when bleeds occur in a target joint, or joint/area with a risk of significant sequelae (e.g., hip, head, GI bleed, etc.). A minor dose is defined as a correction of clotting factor that achieves a level of 30- 60% clotting factor activity that is utilized to treat a bleeding episode that is treated early, in a non-critical area and treatable with a lower hemostatic level (e.g., early non-major joints, small muscle bleeds, and skin/soft tissue, etc.).(4) The Medical and Scientific Advisory Council (MASAC) and National Hemophilia Foundation (NHF) guidelines on treatment of hemophilia B recommend Recombinant FIX (rFIX) products over plasma-derived products as the treatment of choice.(5) In view of the demonstrated benefits of prophylaxis (regular/scheduled administration of clotting factor concentrate to prevent bleeding) begun at a young age in persons with hemophilia B, MASAC recommends that prophylaxis be considered optimal therapy for individuals with severe hemophilia B (Factor IX less than 1%). Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding), with the aim of keeping the trough FIX level above 1% between doses. Optimal dosing and frequency should be determined for each individual by appropriate laboratory monitoring. It is also recommended that individuals on prophylaxis have regular follow-up visits to evaluate joint status, to document any complications such as inhibitors, and to record any bleeding episodes that occur during prophylaxis.(6)

Gene Therapy	Adeno-associated virus (AAV)- mediated gene therapy is increasingly recognized for its potential to treat many monogenic diseases, including hemophilia A and B, by means of delivery of complementary DNA encoding functional Factor VIII or Factor IX proteins, respectively.(7) Numerous human Phase 1/2 clinical trials for hemophilia B and A have been conducted over the past decade. These trials have incorporated modifications of promoters, transgenes, and adeno-associated virus (AAV) vector serotypes, resulting in varying adverse events and levels of Factor IX or Factor VIII. More Phase 1/ 2 trials are in planning stages, including with different transgene delivery systems (e.g., lentiviral vectors). Further, four Phase 3 trials, 2 each in Hemophilia B and A are underway. While the initial results offer the prospect of a potential cure for hemophilia, many questions regarding efficacy and safety remain.(8) Most ongoing trials have shown transient hepatic enzyme elevations, signifying toxicity, in at least a subset of clinical trial participants. The mechanisms behind this toxicity are not fully understood, but include:(8) • An immune response to vector capsid • Possible direct cellular toxicity due to stress from catabolizing the AAV capsid • A cellular stress response due to high transgene protein synthesis burden and/or • Hepatotoxicity resulting from interaction of vector and co- administered potentially hepatotoxic medications, e.g., efavirenz While the mechanisms are not all understood, these adverse events support the need to counsel patients receiving gene therapy to avoid potentially hepatotoxic therapies such as within HAART and support the need for more studies to determine the mechanisms of liver toxicity complicating gene therapy.(8) The Medical and Scientific Advisory Council (MASAC) of NHF continues to emphasize the careful consideration of advances in gene therapy to quantify and mitigate the risks to patients and others, including evaluation in informative animal models (e.g., primates). MASAC supports human clinical trials that proceed with appropriate risk/benefit analysis and risk reduction. MASAC encourages continued research efforts to pursue adequate gene expression to achieve an absence of bleeding events without concern for hepatic and other injury. MASAC strongly suggests the sponsors of gene therapy clinical trials address the relevant

	unknowns during the clinical trial process, including but not limited to:(8) • Opportunities to treat subjects with pre-existing capsid antibodies • Develop strategies to re-treat clinical trial participants • Address potential liver damage short term and long term, including biopsy of treated livers • Durability of response • Clotting factor activity discrepancies • Genomic integration events • Strategies to treat children and • Confounders unique to the hemophilia population, including HIV, hepatitis, and the drugs used for treatment of these disorders • Use of other hepatotoxic agents, such as alcohol and acetaminophen should be carefully evaluated, especially during early timepoints following administration of AAV Each patient should receive individualized discussions whether gene therapy is an option for them. Not all patients are candidates for gene therapy and not all patients who are candidates for gene therapy will want to undergo it. Some recommendations for who are candidates for gene therapy are as follows:(9) • Patients who have a need for a significant improvement of therapy • Patients who require better protection than they are receiving with existing therapies such as: o Very active patients o Patients with increased bleeding by severely damaged joints o Patients with increased bleeding by anticoagulation o Elderly patients: need for anticoagulation, risk for falls • Patients who have problems with continuing with existing therapy • Patients who need to become independent from regular treatment Many gene therapy trials exclude patients who have HIV or AIDS. Some practitioners believe that patients with HIV who are well controlled would benefit from gene therapy. The World Health Organization (WHO) states that anti-retroviral therapy (ART) should be started for all individuals with HIV regardless of WHO clinical stage or CD4 count. Routine viral load and CD4 count monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART. CD4 cell count monitoring can be stopped in individuals who are

	stable on ART and virally suppressed (viral load undetectable).(10-11) Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (i.e., two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.(10-11) The Institute For Clinical And Economic Review (ICER) published a draft evidence report on gene therapy for hemophilia B on September 13,2022. Patients treated with etranacogene dezaparvovec had an 80% reduction in treated joint bleeds and similar reductions in other bleeds when compared with their bleeding rates on factor prophylaxis prior to gene therapy. No patients successfully treated with etranacogene dezaparvovec had to go back on factor prophylaxis during the first 18 months of therapy. It is not yet clear that the initial increase in the Factor IX levels will be maintained for decades, though results are encouraging. Because of the uncontrolled study design, small numbers of patients studied and relatively short follow- up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with Factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. ICER rated etranacogene dezaparvovec as a B+ compared with Factor IX prophylaxis.(12)
Efficacy	Hemgenix (etranacogene dezaparvovec-drlb) is an adeno-associated virus serotype 5(AAV5) based gene therapy designed to deliver a copy of a gene encoding the Padua variant (variant R338L) of human coagulation Factor IX (hFIX-Padua). It is a one-time infusion of the highly active Padua variant of the gene for Factor IX into cells in the liver, resulting in cell transduction and increase in circulating Factor IX activity in patients with hemophilia B.(1) The key trial ICER used for evaluation of etranacogene dezaparvovec was the Phase 3 HOPE-B trial. In addition, results from a Phase 2b trial with 3 patients was used in the assessment. Both studies are single-arm trial that included males with moderately severer to severe hemophilia B. The annualized bleeding rate at 52 weeks was assessed as a primary outcome in the HOPE-B while Factor IX activity was considered as a primary outcome for the Phase 2b trial.(12) The inclusion criteria for the HOPE-B trial included:(13) • Male

	• Age greater than or equal to 18 years of age • Diagnosis of congenital hemophilia B, classified as severe or moderately severe, and currently on Factor IX prophylaxis • Greater than 150 previous exposure days of treatment for Factor IX protein The exclusion criteria for the HOPE-B trial included:(13) • History of Factor IX inhibitors • Positive Factor IX inhibitor test at screening • Positive human immunodeficiency virus (HIV) 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 • Receipt of an experimental agent within 60 days prior to screening • Current participation or anticipated participation within one year after study drug administration in this trial in any other interventional clinical trial involving drugs or devices The efficacy of Hemgenix was evaluated in a prospective, open-label, single-dose, single-arm, multi-national study in 54 patients. The subjects prospectively completed a lead-in period of at least six months with the intent to receive standard of care routine Factor IX prophylaxis. The subjects then received the indicated single intravenous dose of Hemgenix. and followed up monthly until Month 12, then at 6-month intervals until Year 5.(1) The main efficacy outcome was a non-inferiority test of annualized bleeding rate (ABR) during Months 7 to 18 after Hemgenix treatment compared with ABR during the lead-in period. All bleeding episodes, regardless of investigator assessment, were counted. Subjects were allowed to continue prophylaxis during Months 0 to 6. The estimated mean ABR during Months 7 to 18 after Hemgenix treatment was 1.9 bleeds/year with a 95% confidence interval (CI) of (1.0, 3.4), compared with an estimated ABR of 4.1 (95% CI: 3.2, 5.4) during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment/lead-in) was 0.46 (95% CI: 0.26, 0.81), demonstrating non-inferiority or ABR during Month 7 to 18 compared to the lead-in period.(1)
Safety	Hemgenix has no FDA labeled contraindications.

REFERENCES

Number	Reference
1	Hemgenix Prescribing Information. CSL Behring LLC. November 2022.
2	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Hemophilia B. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b.
3	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
4	Medical and Scientific Advisory Committee. MASAC recommendation regarding doses of clotting factor concentrate in the home. MASAC Document #242. June 2016.
5	Medical and Scientific Advisory Council (MASAC) MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Document #263. September 2020.
6	Medical and Scientific Advisory Committee. MASAC recommendation concerning prophylaxis. MASAC Document #241. February 2016.
7	Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med 2020; 382:29-40.
8	Medical and Scientific Advisory Committee. MASAC Document Regarding Risks of Gene Therapy Trials for Hemophilia. Document #254. December 2018.
9	Pipe Steven, VandenDriessche T, Pasi J, Miesbach W. Moving Beyond Factor: Shifting the Paradigm in Hemophilia Through Gene Therapy. Medscape Education Series. Presented through a collaboration between the National Hemophilia Foundation and Medscape. December 2019. Accessed at https://www.medscape.org/viewarticle/922905
10	World Health Organization (WHO) Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. 2016 update.
11	World Health Organization (WHO) Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. June 2016.
12	ICER Institute for Clinical and Economic Review. Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value. Draft Evidence Report. September 13, 2022.
13	HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients. Accessed at HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients - Full Text View - ClinicalTrials.gov

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J1411	Hemgenix	etranacogene dezaparvovec-drlb iv susp	10 x 10 ML ; 11 x 10 ML ; 12 x 10 ML ; 13 x 10 ML ; 14 x 10 ML ; 15 x 10 ML ; 16 x 10 ML ; 17 x 10 ML ; 18 x 10 ML ; 19 x 10 ML ; 20 x 10 ML ; 21 x 10 ML ; 22 x 10 ML ; 23 x 10 ML ; 24 x 10 ML ; 25 x 10 ML ; 26 x 10 ML ; 27 x 10 ML ; 28 x 10 ML ; 29 x 10 ML ; 30 x 10 ML ; 31 x 10 ML ; 32 x 10 ML ; 33 x 10 ML ; 34 x 10 ML ; 35 x 10 ML ; 36 x 10 ML ; 37 x 10 ML ; 38 x 10 ML ; 39 x 10 ML ; 40 x 10 ML ; 41 x 10 ML ; 42 x 10 ML ; 43 x 10 ML ; 44 x 10 ML ; 45 x 10 ML ; 46 x 10 ML ; 47 x 10 ML ; 48 x 10 ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Hemgenix	etranacogene dezaparvovec-drlb iv susp	10 x 10 ML ; 11 x 10 ML ; 12 x 10 ML ; 13 x 10 ML ; 14 x 10 ML ; 15 x 10 ML ; 16 x 10 ML ; 17 x 10 ML ; 18 x 10 ML ; 19 x 10 ML ; 20 x 10 ML ; 21 x 10 ML ; 22 x 10 ML ; 23 x 10 ML ; 24 x 10 ML ; 25 x 10 ML ; 26 x 10 ML ; 27 x 10 ML ; 28 x 10 ML ; 29 x 10 ML ; 30 x 10 ML ; 31 x 10 ML ; 32 x 10 ML ; 33 x 10 ML ; 34 x 10 ML ; 35 x 10 ML ; 36 x 10 ML ; 37 x 10 ML ; 38 x 10 ML ; 39 x 10 ML ; 40 x 10 ML ; 41 x 10 ML ; 42 x 10 ML ; 43 x 10 ML ; 44 x 10 ML ; 45 x 10 ML ; 46 x 10 ML ; 47 x 10 ML ; 48 x 10 ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of congenital hemophilia B (also known as Factor IX deficiency, Christmas disease) **AND** 2. ONE of the following: A. The patient's sex is male **OR** B. The prescriber has provided information that the requested agent is medically appropriate for the patient's sex (medical records required) **AND** 3. The patient is 18 years of age or over **AND** 4. The patient has been screened for Factor IX inhibitor titers AND ONE of the following: (medical records required) A. The patient tested negative for Factor IX inhibitor titers on the initial screening **OR** B. BOTH of the following: 1. The patient tested positive for Factor IX inhibitors on the initial screening **AND** 2. The patient tested negative for Factor IX inhibitors within 2 weeks of initial screening **AND** 5. ONE of the following: (medical records required) A. The patient is on prophylactic therapy with a Factor IX agent (e.g., AlphaNine SD, Alprolix, BeneFIX, Idelvion, Ixinity, Mononine, Profilnine SD, Rebinyn, Rixubis) **OR** B. The patient has current or historical life-threatening hemorrhage **OR** C. The patient has had repeated, serious spontaneous bleeding episodes

Module	Clinical Criteria for Approval
	AND 6. The prescriber has evaluated the patient's liver function and determined the patient has adequate liver function to receive the requested agent based on the following assessments: A. Liver enzyme testing (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin) **AND** B. Hepatic ultrasound and elastography **AND** C. If the patient has sustained liver enzyme elevations and/or radiological liver abnormalities, the prescriber has considered consultation with a specialist (i.e., hepatologist) **AND** 7. The patient has NOT had any previous gene therapy (including requested agent) **Length of Approval:** 1 course per lifetime

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

REVISIONS	
05-05-2023	Policy added to the bcbsks.com web site.
10-02-2023	Policy reviewed by Prime Therapeutics LLC with no revisions.