New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Hemgenix® (etranacogene dezaparvovec-drlb) [CSL Behring]**
Dosage Formulations:	Sterile, preservative-free, clear, and colorless suspension, administered as an intravenous infusion.
FDA Approval Date: **FDB File Date:**	FDA: November 22, 2022 FDB: December 4, 2022
Indication:	Treatment of adults with hemophilia B who • Currently use Factor IX (FIX) prophylaxis therapy, or • Have current or historical life-threatening hemorrhage, or • Have repeated, serious spontaneous bleeding episodes.
Mechanism of Action:	Hemgenix uses a modified adeno-associated virus 5 (AAV5) to deliver a highly functional copy of the FIX gene, called FIX-Padua, to patients' hepatic cells, the body's main producers of clotting factors. The FIX-Padua gene version was shown to result in FIX clotting activity five to eight times greater than the activity normally associated with the FIX gene. As such, the therapy — given as a one-time infusion directly into the bloodstream — is expected to increase FIX levels, helping to prevent and control bleeding for long periods of time.
Dose/ Administration:	• Before initiating Hemgenix perform Factor IX inhibitor titer testing. In response to a positive test result, perform a retest in approximately 2 weeks. If both test results are positive, Hemgenix should not be administered. • Liver function tests should be performed, including baseline evaluation of AST (aspartate aminotransferase), ALT (alanine aminotransferase), alkaline phosphatase (ALP), and total bilirubin. • Hepatic ultrasound and elastography should also be performed to assess liver health • Hemgenix is supplied as a customized kit. Each kit contains 10 to 48 single-use Hemgenix 10 mL vials, at a concentration of 1×10^{13} genome copies (gc) per mL. • The recommended dose of Hemgenix is 2×10^{13} gc per kg. (or 2mL/kg). • To calculate the number of vials needed, calculate the patient's dose in milliliters and divide by a factor of 10. • Sample dose calculation:

Patient Weight	Dose (mL) (body weight multiplied by 2)	Vials Needed (divide by 10; round up)
84 kg	168 mL	17 vials

- Preparation and Administration
  - The Hemgenix dose is diluted in 500 mL of 0.9% sodium chloride prior to administration
    - If patient is greater than or equal to 120 kg, the Hemgenix dose is to be divided in half and administered in two separate 500mL bags of 0.9% sodium chloride
    - In either case, a volume of 0.9% sodium chloride equal to the volume of Hemgenix is to be removed from the bag(s) prior to dilution
  - Hemgenix vials should be inspected for particulates or discoloration prior to administration
  - Vials should be gently swirled 3 times (10 seconds) in order to homogenize the suspension. Hemgenix vials should NOT be shaken.
  - Using aseptic technique, withdraw Hemgenix suspension from each vial using a 20 mL luer-lock or larger syringe. Inject each 10mL amount into the bag of 0.9% sodium chloride until volume is brought back up to 500 mL.
  - Invert the bag at least 3 times to ensure even distribution of the medication. Protect the bag from light until infusion is complete.

Disease State Clinical Highlights:

- Hemophilia is caused by a single pathogenic variant, which results in insufficient production of hepatically synthesized clotting factors. Insufficient circulating clotting factors can lead to major and minor bleeding that can cause significant morbidity and mortality. Because it is an X-linked recessive hereditary disease it primarily presents in male children of female carriers. There are two main types of hemophilia - hemophilia A and hemophilia B.
- Hemophilia A is characterized by a deficiency of clotting Factor VIII (FVIII).
- Hemophilia B is characterized by a deficiency in clotting Factor IX.
- The estimated prevalence of hemophilia in the United States is 12 cases per 100,000 males for hemophilia A and 3.7 cases per 100,000 males for hemophilia B.
- The estimated incidence of hemophilia among U.S. births is 1 birth per 5,617 male births for hemophilia A and 1 birth per 19,283 male births for hemophilia B.
- Hemophilia severity classification:

Disease Severity	Clotting Factor Level
Severe	<1 IU/dL or <1% of normal
Moderate	1-5 IU/dL or 1-5% of normal
Mild	5-40 IU/dL or 5% to <40% of normal

- Generally, patients with severe hemophilia can develop spontaneous bleeds even in the absence of trauma. Conversely, patients with mild hemophilia usually do not bleed unless a traumatic event is experienced. Amongst all patients with hemophilia, approximately 4 in 10 have the severe form of the disease.
- Patients with hemophilia can experience bleeding into joint spaces. The main joints that can be affected include the elbows, knees, and ankles. This type of bleeding can lead to increased swelling, severe pain, deformity, and osteoarthritis. Severe cases could require total joint replacement to correct these manifestations.
- Overall Medicaid spending on hemophilia B treatment was reported by the Centers for Medicare & Medicaid Services (CMS) to be 1.59 billion dollars in 2019.

Drug Clinical Highlights

- Hemgenix is the first and only gene therapy developed and approved by the FDA for treatment of hemophilia B.

Contraindications:

- None

Warnings/Precautions:

- Infusion reactions
  - Patients reported symptoms such as headache, abdominal pain, lightheadedness, flushing, rash development, and hypertension during infusion.
  - Patients should be monitored during Hemgenix administration and for at least 3 hours after the end of the one-time infusion.
  - If symptoms manifest, stop or slow the infusion. Restart infusion at a slower rate once symptoms resolve.
- Hepatotoxicity
  - Serum transaminase levels should be monitored once per week for 3 months after Hemgenix administration. Patients who experience an elevation in liver enzymes should continue to be monitored weekly until levels return to baseline.
  - Transaminitis (especially within the first three months after Hemgenix administration) is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the efficacy of Hemgenix and other AAV-vector based gene therapy.
- Hepatocellular carcinoma
  - Annual liver ultrasound and alpha-fetoprotein testing should be performed on patients who have preexisting risk factors, including but not limited to cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease (NAFLD), chronic

alcohol consumption, non-alcoholic steatohepatitis (NASH), or advanced age.
- Neutralization of AAV5 vector capsid
  - Patient with preexisting neutralizing anti-AAV antibodies could hinder transgene expression. In the HOPE-B trial (summarized below), anti-AAV5 antibodies were detected using an unvalidated clinical trial assay. Patients with detectable antibodies showed mean Factor IX activity that was numerically lower than subjects without detectable antibodies.

Pregnancy/Lactation:
- Hemgenix is not intended for administration in women.

Clinical Studies:
- HOPE-B (NCT03569891): an ongoing, multi-center, open-label, single-dose, multinational trial to demonstrate the efficacy of Hemgenix and to further evaluate its safety.
  - HOPE-B is enrolling adult males between the ages of 19 and 75 years diagnosed with severe or moderately severe hemophilia B. Subjects receive a single dose of Hemgenix, 2 x 10^{13} gc/kg and enter a 5-year follow-up period.
  - The trial began in June 2018 and has an estimated completion date of March 2025. 54 subjects were included in the safety and efficacy analysis at the time Hemgenix was FDA-approved.
- Inclusion Criteria
  - Male
  - Age ≥ 18 years
  - Diagnosis of congenital hemophilia B, classified as severe or moderately severe, and currently receiving Factor IX prophylaxis
  - >150 previous exposure days of treatment with factor IX protein
- Exclusion Criteria
  - History of Factor IX inhibitors
  - Positive Factor IX inhibitor test at screening
  - Select screening laboratory value >2 times the upper limit of normal
  - Positive human immunodeficiency virus (HIV) at screening, not controlled by anti-viral therapy
  - Active hepatitis B or C infection
  - 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 or anticipated participation within one year after study drug administration in the HOPE-B trial or any other interventional clinical trial involving drugs or devices
- Baseline Demographics

HOPE-B (NCT03569891)	**n = 54**
Age, mean (SD, min-max), years	41.5 (15.8, 19-75)
Severity of hemophilia B, n (%) - Severe - Moderately severe	 44 (81.5) 10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior Hepatitis B infection, n (%)	3 (5.6)
Prior Hepatitis C infection, n (%)	31 (57.4)
Pre-screening FIX replacement, n (%) - Extended half-life - Standard half-life	 31 (57.4) 23 (42.6)
Detectable AAV5 antibodies, n (%)	23 (42.6)

- Primary Outcome
  - Non-inferiority test of Annualized Bleeding Rate (ABR), comparing months 1 through 6 of the lead-in period with months 7 through 18 after Hemgenix treatment

	Lead-in Period	Months 7 through 18 after Hemgenix administration
All Bleeds	136	96
Follow-up time (Person-Year)	33	52
Mean Adjusted ABR (95% CI)	4.1 (3.2 – 5.4)	1.9 (1.0 – 3.4)
Subjects with Bleeds	40 (74%)	20 (37%)
Subject with Zero Bleeds	14 (26%)	34 (63%)
Observed Spontaneous Bleed Count	50 (37%)	14 (26%)
Observed Joint Bleed Count	77 (57%)	19 (35%)

Adverse Events:

- The most frequently reports adverse events are summarized in the table below.

Adverse Reaction	Subjects (%) (n = 57)
Alanine aminotransferase increased	24 (42%)
Aspartate aminotransferase increased	24 (42%)
Blood creatine kinase increased	24 (42%)
Infusion-related reactions	19 (33%)
Headache	10 (18%)
Flu-like symptoms	8 (14%)
Malaise	7 (12%)
Fatigue	7 (12%)
Nausea	4 (7%)
Hypersensitivity	2 (4%)

- One patient died of cardiogenic shock and urosepsis deemed unrelated to Hemgenix treatment.
- One patient only received 10% of the Hemgenix dose due to an infusion-related reaction.

Price Per Unit (WAC):

$3.5 million per Hemgenix kit

Therapeutic Alternatives:

- Hemgenix represents the first gene-based therapy FDA approved for Hemophilia B.
- The primary treatment of hemophilia B is replacement of the deficient Factor IX, either through preventative infusions (prophylaxis) or on-demand therapy.
- Factor IX products:

Standard Half-Life Products	Elimination Half-Life
BeneFIX®	16-19 hours
Ixinity®	24 hours
Rixubis®	23-26 hours
Extended Half-Life Products	
Alprolix®	54-90 hours
Idelvion®	104 hours
Rebinyn®	103-115 hours

Plasma-Derived Products	
AlphaNine®	18 hours
Mononine®	23 hours

- The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) recommends prophylaxis be considered for individuals 1 year of age and older with severe hemophilia B. Prophylactic therapy should be instituted prior to the onset of frequent bleeding, with the aim of keeping the trough Factor IX level above 1% between doses.
- Approximately 1 to 6 percent of patients with hemophilia B develop inhibitors. These are antibodies that attack the infused factor product which renders it inactive.
- Immune tolerance induction (ITI) is the primary method used to eliminate or control inhibitors. It involves administering repeated doses of factor to tolerize the patient's immune system to the factor and reduce antibody production. If initial ITI is unsuccessful, immune suppression with cyclophosphamide or rituximab may be used.
- ITI is unsuccessful in 20 to 30 percent of patients with hemophilia B who develop inhibitors. Those patients would be candidates for bypass agents (BPAs), which contain an activated form of a clotting factor downstream of Factor IX. These products, when used as weekly prophylaxis, have a cost burden of $300,000 to $3,000,000 per year.

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:
- Participant is male **AND**
- Aged ≥ 18 years **AND**
- Documented diagnosis of moderately severe or severe hemophilia B (ICD10 D67) **AND**
- Diagnosis is confirmed by documentation of a clotting factor 1-2% of normal **AND**
- Documentation of a negative Factor IX inhibitor titer test

Denial Criteria:
- Participant has a documented diagnosis of mild or moderate hemophilia B confirmed by clotting factor > 2% of normal.

Continuation of Therapy:
- Not applicable; Hemgenix is a one-time intravenous infusion

Additional Provider Diagnostic/Monitoring Criteria, if desired:
- Baseline AST/ALT, then weekly for 3 months after administration. If participant experiences elevations, these should be regularly monitored until a return to baseline
- Baseline Factor IX activity, then weekly for 3 months after administration
- Baseline alkaline phosphatase
- Baseline total bilirubin
- Baseline blood creatine kinase
- Hepatic ultrasound and elastography done within 6 months prior to administration
- Annual hepatic ultrasound and alpha-fetoprotein testing in patients with preexisting risk factors for hepatocellular carcinoma
- Factor IX inhibitor testing should be performed if participant experiences uncontrolled bleeding or if their plasma Factor IX levels decrease post-infusion

Implication to State Medicaid Program:	• LOE: 2034-2035
	• Based on its specialized use and cost, Hemgenix should ideally be administered in a hemophilia treatment center (HTC). There are six such facilities in Missouri; 1 each in Kansas City and Columbia, and four in St. Louis.
	• CSL Behring has created a prescription form that is to be used every time Hemgenix is prescribed. It acts as the official prescription and also includes sections to be filled out regarding insurance information, patient demographics, and HTC information.
	  ○ Prescriber can choose purchase method:
	  ▪ Directly from CSL Behring
	  ▪ Through the Hemgenix Specialty Pharmacy Network
	• CSL Behring has also created Hemgenix Connect℠, a collection of services designed to serve as a resource if eligible participants have questions about therapeutics, insurance coverage, travel, or other topics related to the utilization of Hemgenix.
	
	Roctavian™ (valoctocogene roxaparvovec) [BioMarin]
	• Roctavian is the first gene therapy developed for treatment of hemophilia A (Factor VIII deficiency).
	• It is being evaluated in the Phase 3 GENEr8-1 study (NCT03370913). Preliminary results show that Roctavian demonstrated treatment benefits after one year:
	  ○ Mean yearly Factor VIII use decreased by 99%
	  ○ Mean treated bleeding rates after week 4 decreased by 84%
	• In August of 2022, Roctavian was granted conditional marketing authorization by the European Commission
	• BioMarin is also evaluating Roctavian in patients with AAV5 antibodies, Factor VIII inhibitors, and those treated with corticosteroids.
	• PDUFA date: 6/30/2023

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