NEW DRUG APPROVAL

Brand Name	Hemgenix®
Generic Name	etranacogene dezaparvovec-drlb
Drug Manufacturer	CSL Behring

New Drug Approval

FDA Approval Date: November 22, 2022

Review designation: N/A

Type of review: N/A

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

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, a change in a gene.

People with hemophilia B bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures or trauma. How frequently a person bleeds and how serious the bleeds are depending on how much FIX is in the plasma, the straw-colored fluid portion of blood.

Normal plasma levels of FIX range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person's symptoms.

- **Mild hemophilia B. 6% up to 49% of FIX in the blood: -** People with mild hemophilia B typically experience bleeding only after serious injury, trauma or surgery. In many cases, mild hemophilia is not diagnosed until an injury, surgery or tooth extraction result in prolonged bleeding. The first episode may not occur until adulthood. Women with mild hemophilia often experience menorrhagia, heavy menstrual periods, and can hemorrhage after childbirth.
- **Moderate hemophilia B. 1% up to 5% of FIX in the blood: -** People with moderate hemophilia B tend to have bleeding episodes after injuries. Bleeds that occur without obvious cause are called spontaneous bleeding episodes.
- **Severe hemophilia B. <1% of FIX in the blood: -** People with severe hemophilia B experience bleeding following an injury and may have frequent spontaneous bleeding episodes, often into their joints and muscles.

According to the US Centers for Disease Control and Prevention, hemophilia occurs in approximately 1 in 5,000 live births. There are between 30,000 – 33,000 people with hemophilia in the US. All races and ethnic groups are affected. Hemophilia B is four times less common than hemophilia A.

Efficacy

The efficacy of Hemgenix® was evaluated in a prospective, open-label, single-dose, singlearm, multi-national study (N = 54). The study enrolled adult male subjects aged 19 to 75 years, with severe or moderately severe Hemophilia B, who received a single intravenous dose of 2×10^{13} gc/kg body weight of Hemgenix® and entered a follow-up period of 5 years. The study is on-going.

The 54 subjects prospectively completed a lead-in period of at least six months with the intent to receive standard of care routine Factor IX prophylaxis. These 54 subjects then received the indicated single intravenous dose of Hemgenix®. Subjects were then followed up monthly until Month 12, and then at 6-month intervals until Year 5. For the efficacy evaluation, data up to 18 months post-treatment were used. Of the 54 subjects, 53 subjects completed at least 18 months of follow-up in the ongoing study. One subject with numerous cardiovascular and urologic risk factors, aged 75 years at screening, died of urosepsis and cardiogenic shock at Month 15 post-dose (at age 77 years) unrelated to treatment. Another subject received around 10% of the intended dose of Hemgenix® due to an infusion-related hypersensitivity reaction.

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 mean 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 of ABR during Months 7 to 18 compared to the lead-in period.

Two subjects were not able to stop routine prophylaxis after Hemgenix® treatment. During Months 7 to 18, an additional subject received prophylaxis from Days 396-534 [approximately 20 weeks].

Table 1. Total Bleeding Events and ABRs (Full Analysis Set: N=54)

	Lead-in Period[a]	Months 7 to 18[b] after Hemgenix® treatment
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%)

Abbreviations: ABR = Annualized Bleeding Rate; CI = Confidence Interval

[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 Hemgenix® 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.

Safety

ADVERSE EVENTS

The safety of Hemgenix® was evaluated in two clinical studies (the first study enrolled 3 subjects and the second study 54 subjects). Both studies enrolled adult male subjects with moderately severe or severe Hemophilia B (N = 57), who received a single intravenous dose of 2 × 1013 461 gc/kg body weight of Hemgenix®. All subjects entered a follow-up period of 5, years.

No serious adverse reactions were reported.

The most common 465 adverse reactions observed in ≥5% of subjects post-dose are.

Adverse Reactions ≥5%	Subjects (%) (N = 57)
Alanine aminotransferase increased	24 (42%)
Headache	10 (18%)
Blood creatine kinase increased	24 (42%)
Flu-like symptoms	8 (14%)
Infusion-related reactions*	19* (33%)
Hypersensitivity	2** (4%)
Fatigue	7 (12%)
Aspartate aminotransferase increased	24 (42%)
Nausea	4 (7%)
Malaise	7 (12%)

Infusion-related reaction: In 7 subjects symptoms occurred during infusion, in 12 subjects after infusion. Symptoms occurring in ≥ 5% of subjects were: Dizziness, Flu-like symptoms and Headache. Symptoms occurring in < 5% of subjects were: Abdominal pain, Abdominal discomfort, Chest discomfort, Chills, Eye pruritus, Fever (Pyrexia), Flushing, Hives (Urticaria), Infusion site reaction, and Tachycardia. Eleven subjects recovered on the day or day one after infusion. Eight subjects recovered within 8 days after infusion.

**1of 2 hypersensitivity reactions - 12 minutes after initiation of administration of Hemgenix®, the patient experienced high blood pressure, red eyes, feeling warm, dizziness, coughing, dyspnea, elevated heart rate, shivering, and leg cramps. Infusion was stopped and not restarted. Only 10% of the Hemgenix® dose was administered. The patient recovered on the same day after treatment with intravenous diphenhydramine and intramuscular epinephrine.

WARNINGS & PRECAUTIONS

- **Infusion reactions:** Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.
- **Hepatotoxicity:** Closely monitor transaminase levels once per week for 3 months after Hemgenix® administration to mitigate the risk of potential hepatotoxicity. Continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline. Consider corticosteroid treatment should elevations occur.

- **Hepatocellular carcinogenicity:** For patients with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease (NAFLD), chronic alcohol consumption, non-alcoholic steatohepatitis (NASH), and advanced age), perform regular (e.g., annual) liver ultrasound and alpha-fetoprotein testing following administration.
- **Monitoring Laboratory tests:** Monitor for Factor IX activity and Factor IX inhibitors.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Hemgenix® is an adeno-associated virus serotype 5 (AAV5) based gene therapy designed to deliver a copy of a gene encoding the Padua variant of human coagulation Factor IX (hFIX598 Padua). Single intravenous infusion of Hemgenix® results in cell transduction and increase in circulating Factor IX activity in patients with Hemophilia B.

Dose & Administration

ADULTS

The recommended dose of Hemgenix® is 2 x 1013 genome copies (gc) per kg of body weight.
Administer Hemgenix® as an intravenous infusion after dilution with 0.9% normal saline at a constant infusion rate of 500 ml/hour (8 mL/min).

PEDIATRICS

None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Hemgenix® is provided in a kit containing 10 to 48 vials. Each kit constitutes a dosage unit 319 based on the patient's body weight.

Hemgenix® has a nominal concentration of 1 x 1013 321 gc/mL, and each vial contains an 322 extractable volume of not less than 10 mL.