CSL Behring

Product information for hospitals

Important Safety Information

Warning and Precautions

Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. 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/Hepatocellular Carcinoma

Post-dose, monitor for elevated transaminase levels. Consider corticosteroid treatment should elevations occur. The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors for hepatocellular carcinogenicity, perform regular (eg, annual) abdominal ultrasound and alpha-fetoprotein testing following administration.

Immune-mediated neutralization of the AAV5 vector capsid

Preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired levels.

Monitoring Laboratory Tests

In addition to monitoring liver function, monitor for Factor IX activity and Factor IX inhibitors after administration.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

Healthcare Systems

HEMGENIX®
etranacogene dezaparvovec-drlb

Product information overview

1. AHFS CLASSIFICATION NUMBER

Gene therapy: 26:12; 20:28.16 hemostatics[1]

2. GENERIC NAME

Etranacogene dezaparvovec-drlb suspension, for intravenous infusion

3. SOURCE OF SUPPLY

HEMGENIX is manufactured by uniQure Inc.

4. BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

BLA 125772/0, November 22, 2022[2]

5. PHYSICAL PROPERTIES

a. Macroscopic appearance

HEMGENIX is a clear and colorless suspension for intravenous infusion.

HEMGENIX is provided in a kit containing 10 to 48 single-use vials. Each kit constitutes a dosage unit based on the patient's body weight.

HEMGENIX has a nominal concentration of 1×10^{13} gc/mL, and each vial contains an extractable volume of not less than 10 mL.

b. Solubility

HEMGENIX is formulated as a sterile, preservative-free, clear, and colorless suspension for intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline).

6. CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

N/A

b. Recommended storage and handling conditions for HEMGENIX

HEMGENIX is shipped at 2 °C to 8 °C (36 °F to 46 °F).

Upon receipt, store HEMGENIX vials in a refrigerator at 2 °C to 8 °C (36 °F to 46 °F). Store HEMGENIX in the original carton until use. Protect HEMGENIX from light until time of dilution and administration. Do NOT FREEZE.

Once diluted, store HEMGENIX in the infusion bag protected from light.

Store diluted HEMGENIX in the infusion bag at 15 °C to 25 °C (59 °F to 77 °F). Infuse the diluted product within 24 hours after the dose preparation.

c. Excipients contained in the commercially available product

HEMGENIX is formulated with the following excipients: sucrose (50 mg/mL), polysorbate-20 (0.22 mg/mL), potassium chloride (0.2 mg/mL), potassium phosphate (0.2 mg/mL), sodium chloride (8 mg/mL), and sodium phosphate (1.2 mg/mL). HEMGENIX contains no preservative.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

Product information overview (cont'd)

7. PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

HEMGENIX is an adeno-associated virus serotype 5 (AAV5)–based gene therapy.

b. Mechanism of action

HEMGENIX is designed to deliver a copy of a gene encoding the Padua variant of human coagulation factor IX (hFIX-Padua). Single intravenous infusion of HEMGENIX results in cell transduction and increases in circulating factor IX activity in patients with hemophilia B.

c. Pharmacokinetic data

Vector biodistribution (within the body) and vector shedding (excretion/secretion).

Non-clinical data

Biodistribution of HEMGENIX was evaluated after intravenous administration in healthy male mice and non-human primates. The highest levels of vector DNA were detected in the liver and adrenal glands in both species. Vector DNA was also detected in all reproductive tissues examined (epididymis, seminal vesicles, and testes). In a mating study evaluating a predecessor of HEMGENIX, transmission of vector DNA to naïve female mice following mating with dosed males was not observed.

Clinical data

Following administration of the predecessor of HEMGENIX at doses of 5×10^{12} (N=5) and 2×10^{13} gc/kg (N=5) in a clinical study, the pharmacokinetics of vector DNA in blood and viral shedding in saliva, nasal secretions, semen, urine, and feces were characterized. Clearance of vector DNA as confirmed by 3 subsequent measurements below limit of detection (LOD) was achieved in all subjects at both dose levels from all the matrices except for semen, where clearance was achieved in 9 out of 10 subjects. One subject was unable to produce semen due to a historical medical condition and, therefore, shedding from semen could not be assessed. The maximum time to clearance of vector DNA was 22 weeks for urine, 26 weeks for saliva and nasal secretions, 40 weeks for feces, 52 weeks for semen, and 159 weeks for blood.

Subsequently, the pharmacokinetics of vector DNA in blood and viral shedding in semen following HEMGENIX administration were characterized in 2 clinical studies.

In an initial clinical study (N=3), clearance of vector DNA from semen and blood (ie, confirmed with 3 subsequent measurements below LOD of vector DNA) was achieved in 2 out of 3 subjects, and achieved in all subjects after 3 years post administration. One subject did not return the required number of semen samples to assess the shedding status as per the definition of 3 subsequent measurements below LOD of vector DNA.

In the clinical efficacy study (N=54), a total of 56% (30/54) of subjects achieved absence of vector DNA from blood and 69% (37/54) from semen by month 24. Several subjects did not return the required number of blood and semen samples to assess the shedding status as per the definition of 3 subsequent measurements below LOD of vector DNA. Considering results obtained from 2 available consecutive samples below LOD, a total of 74% (40/54) and 87% (47/54) subjects were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post administration.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

Product information overview (cont'd)

8. DOSAGE RANGE

a. Dosage range and route of administration

HEMGENIX is for single-use intravenous infusion after dilution only.

- The recommended dose of HEMGENIX is 2 x 10^{13} genome copies (gc) per kilogram (kg) of body weight (or 2 mL/kg body weight) administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline). Calculate the dose as follows:

HEMGENIX dose (in mL) = patient body weight (in kg) x 2

The multiplication factor 2 represents the per kilogram dose (2 x 10^{13} gc/kg) divided by the amount of genome copies per mL of the HEMGENIX solution (1 x 10^{13} gc/mL).

Number of HEMGENIX vials needed = HEMGENIX dose (in mL) divided by 10 (round up to the next whole number of vials).

The division factor 10 represents the extractable volume of HEMGENIX from each vial (10 mL).

The total volume of the patient's HEMGENIX dose to be diluted may be less than the total volume of vials needed.

Example calculation for 72 kg patient

Patient weight	HEMGENIX dose (mL) (body weight multiplied by 2)	Number of vials needed (HEMGENIX dose [mL] divided by 10, then rounded up)
72 kg	144 mL	15

- HEMGENIX can only be administered once
- Each kit constitutes a dosage unit based on the patient's body weight. HEMGENIX has a nominal concentration of 1 x 10^{13} gc/mL, and each vial contains an extractable volume of not less than 10 mL

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

8. DOSAGE RANGE (cont'd)

b. Use in specific populations

Pregnancy

HEMGENIX is not intended for women. No adverse effects on mating rate and fertility indices or fetal weights were observed in healthy naïve female mice mated with healthy male mice that were intravenously administered a predecessor of HEMGENIX product 6 days prior to mating. Vector DNA was not detected in the uterus, placenta, or fetus.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

HEMGENIX is not intended for administration in women.

Females and males of reproductive potential

No clinical studies have been performed to evaluate the effects of HEMGENIX on fertility in humans. Twenty days after intravenous administration of a predecessor of HEMGENIX product in healthy male mice, vector DNA was detected in all reproductive tissues examined (epididymis, seminal vesicles, testes, and sperm). However, no differences were observed in mating rates and fertility indices in healthy naïve female mice following mating with the dosed males.

Pediatric use

The safety and efficacy of HEMGENIX in pediatric patients have not been established.

Geriatric use

The clinical studies included a total of 6 geriatric subjects with hemophilia B, aged 68 to 75 years at time of enrollment. No meaningful differences in the safety and efficacy profile were observed in these subjects compared to subjects aged 18 to 65 years, and no dose adjustment was made.

Hepatic impairment

Limited clinical data in subjects with liver impairment indicate numerically lower factor IX activity as compared to subjects without hepatic impairment. In the clinical studies, no dose adjustment was made in subjects with hepatic pathologies. The safety and efficacy in subjects with advanced hepatic impairment, including cirrhosis, advanced liver fibrosis, or uncontrolled hepatitis B and C, have not been studied.

Renal impairment

Limited clinical data are available in subjects with mild and moderate renal impairment. In the clinical studies, no dose adjustment was made in these subjects. The safety and efficacy in subjects with severe renal impairment and end-stage renal disease have not been studied.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

9. SAFETY

a. Adverse reactions, toxicities, and special precautions

Adverse reactions

The most common adverse reactions (incidence ≥5%) reported in clinical studies were alanine aminotransferase (ALT) elevations, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, malaise, and aspartate aminotransferase (AST) elevations.

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of HEMGENIX was evaluated in 2 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 2×10^{13} gc/kg body weight of HEMGENIX. All subjects entered a follow-up period of 5 years.

No treatment-related serious adverse reactions were reported. The most common adverse reactions observed in ≥5% of subjects post dose are listed in the table below.

Adverse reactions (incidence ≥5%) following treatment with HEMGENIX

Adverse reactions ≥5%	Subjects (%) (N=57[a])
ALT increased	24 (42%)
Headache	10 (18%)
Blood creatine kinase increased	24 (42%)
Flu-like symptoms	8 (14%)
Infusion-related reactions	19[b] (33%)
Hypersensitivity	2[c] (4%)
Fatigue	7 (12%)
AST increased	24 (42%)
Nausea	4 (7%)
Malaise	7 (12%)

[a]N=57 patients (N=3 patients from a phase 2b and N=54 patients from a phase 3 clinical study).

[b]Infusion-related reactions: 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 of or day 1 after infusion. Eight subjects recovered within 8 days after infusion.

[c]1 of 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 re-started. Only 10% of the HEMGENIX dose was administered. The patient recovered on the same day after treatment with intravenous diphenhydramine and intramuscular epinephrine. 2 of 2 hypersensitivity reactions: 10 minutes after initiation of administration of HEMGENIX, the patient experienced itching, tightness of throat, and swelling of the right side of the neck. The HEMGENIX dose was not interrupted and was administered in full. All symptoms resolved on the same day without treatment.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

9. SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Infusion-related reactions were observed in 19 subjects. Infusions were temporarily interrupted in 3 subjects and resumed at a slower infusion rate after treatment with antihistamines and/or corticosteroids. In 1 subject, infusion was stopped and not resumed (see footnote of the table on page 6).

There were 24 subjects who had elevated ALT values from day 8 to 731 post administration.

Five subjects had ALT elevations >2 to 3x the upper limit of normal (ULN) (range: 89 to 130 IU/L), 1 subject had an ALT elevation >3 to 5x ULN (193 IU/L), and 1 subject had an ALT elevation >5x ULN (275 IU/L). The subject who had the ALT elevation >5x ULN occurred 3 weeks after HEMGENIX administration.

Five subjects had AST elevations >2 to 3x ULN (range: 71 to 118 IU/L), 3 subjects had AST elevations >3 to 5x ULN (range: 127 to 163 IU/L), and 1 subject had an AST elevation >5x ULN (327 IU/L). The subject who had the AST elevation >5x ULN occurred 11 months after HEMGENIX administration.

Seventeen subjects had elevations in ALT levels within the first 4 months after HEMGENIX infusion (range: 41 to 275 IU/L). Eleven of these subjects' ALT levels resolved within 4 months post infusion (range: 41 to 275 IU/L) and 5 of these subjects' ALT levels never normalized as of last follow-up (range of values at 2-year follow-up: 48 to 110 IU/L). Seven additional subjects had ALT elevations with onset between months 6 and 24 (range: 42 to 193 IU/L). Five of these subjects had additional risk factors for having elevated transaminase levels, including hepatitis C and human immunodeficiency virus (HIV). ALT levels never normalized as of last follow-up (range of values at 2-year follow-up: 59 to 193 IU/L) in 3 of the subjects with ALT elevations with onset between months 6 and 24.

Nineteen subjects had elevations in AST levels within 3 months after HEMGENIX infusion (range: 32 to 163 IU/L). Nine of these subjects' AST elevations resolved within 4 months post infusion (range: 35 to 163 IU/L), 3 resolved within 7 to 13 months post infusion (range: 35 to 62 IU/L), and 7 of these subjects' AST levels never normalized as of last follow-up (range of values at 2-year follow-up: 36 to 327 IU/L). The remaining 5 subjects with AST elevations had onset of between 6 months and 2 years post infusion (range: 36 to 127 IU/L), and AST levels had not normalized as of the last follow-up for 1 subject (AST at 2-year follow-up: 127 IU/L) who had additional risk factors for having elevated transaminase levels.

Nine subjects with ALT elevations received a tapered course of corticosteroids. The mean duration of corticosteroid treatment for the elevated ALT was 81.4 days. Nineteen of the 24 subjects with ALT elevations also had a related AST elevation. Twenty-one subjects had elevated transaminase levels and were not treated with corticosteroids.

b. Contraindications, warnings, and precautions

Contraindications

None.

Warnings and precautions

Infusion reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. Symptoms may include chest tightness, headaches, abdominal pain, lightheadedness, flu-like symptoms, shivering, flushing, rash, and hypertension. Closely monitor patients for signs or symptoms of an infusion reaction throughout the infusion period and for at least 3 hours after end of infusion. Do not infuse the product faster than 500 mL/hour.

In the event of an infusion reaction during administration, the infusion may be slowed or stopped. If the infusion is stopped, re-start at a slower rate when the infusion reaction has resolved. Consider treatment with a corticosteroid or antihistamine for management of an infusion reaction.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

9. SAFETY (cont'd)

b. Contraindications, warnings, and precautions (cont'd)

Warnings and precautions (cont'd)

Hepatotoxicity

Intravenous administration of a liver-directed AAV vector could potentially lead to liver transaminase elevations (transaminitis). Transaminitis, particularly when observed in the first 3 months after HEMGENIX administration, is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the AAV vector–based gene therapy.

In clinical studies with HEMGENIX, most subjects had asymptomatic and predominantly mild elevations in transaminases. Elevated ALT levels occurred most often in the first 4 months after HEMGENIX administration. There were some subjects who had a late onset of elevated ALT levels between months 6 and 24 (range: 42 to 193 IU/L); however, all of these ALT values were <2x ULN with the exception of 1 subject. Three additional subjects had AST elevations with onset and resolution between months 6 and 12 (range: 41 to 96 IU/L).

In 1 subject, an ALT elevation >5x ULN occurred 24 days after HEMGENIX administration and resolved by 51 days after HEMGENIX administration. There was 1 subject who had an AST elevation >5x ULN that occurred 11 months after HEMGENIX administration and resolved to <2x ULN 8 days later.

The majority of the elevated ALT values returned to baseline; however, 9 subjects' ALT values never resolved to normal (range at 2-year follow-up: 48 to 193 IU/L).

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.

In case of increased ALT levels above the ULN or double baseline levels, consider implementing a course of corticosteroid, along with human factor IX activity monitoring.

Immune-mediated neutralization of the AAV5 vector capsid

In AAV vector–based gene therapies, preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. Following treatment with HEMGENIX all subjects developed neutralizing anti-AAV antibodies. Currently, there is no validated neutralizing anti-AAV5 antibody assay.

In the clinical studies with HEMGENIX, an unvalidated clinical trial assay was utilized to assess preexisting neutralizing anti-AAV5 antibodies. The subject subgroup with detectable preexisting neutralizing anti-AAV5 antibodies up to titers of 1:678 showed mean factor IX activity that was numerically lower compared to that subject subgroup without detectable preexisting neutralizing anti-AAV5 antibodies. Subjects with and without preexisting neutralizing anti-AAV5 antibodies demonstrated hemostatic protection. In 1 subject with a preexisting neutralizing anti-AAV5 antibody titer of 1:3212, no human factor IX expression was observed, and re-start of the exogenous factor IX prophylaxis was needed for bleeding events.

Anti-AAV5 antibody study

Patients who intend to receive treatment with HEMGENIX are encouraged to enroll in a study to measure preexisting anti-AAV5 neutralizing antibodies by calling CSL Behring at 1-800-504-5434. The study evaluates the effect of preexisting anti-AAV5 neutralizing antibodies on the risk of bleeding.

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

9. SAFETY (cont'd)

b. Contraindications, warnings, and precautions (cont'd)

Warnings and precautions (cont'd)

Hepatocellular carcinogenicity

The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. HEMGENIX is composed of a non-replicating AAV5 vector whose DNA persists largely in episomal form. Random integration of HEMGENIX vector DNA to the human DNA at low frequency is possible. No HEMGENIX-associated clonal expansion or carcinogenicity was observed in clinical studies. One subject with preexisting risk factors for developing hepatic cancer developed a hepatocellular carcinoma, which was assessed as not likely related to HEMGENIX treatment based on vector integration site analyses and whole genome sequencing. Patients with preexisting risk factors for hepatocellular carcinoma (eg, patients with cirrhosis, advanced hepatic fibrosis, hepatitis C or B, nonalcoholic fatty liver disease, chronic alcohol consumption, nonalcoholic steatohepatitis, and advanced age) should receive abdominal ultrasound screenings and be monitored regularly (eg, annually) for alpha-fetoprotein elevations in the 5 years following administration.

Monitoring laboratory tests

After HEMGENIX administration, regularly monitor patient's factor IX activity levels. When using an in vitro activated partial thromboplastin time (aPTT)-based one-stage clotting assay (OSA) for determining factor IX activity, plasma factor IX activity results can be affected by both the type of aPTT reagent and the reference standard used in the assay. This is important to consider particularly when changing the laboratory and/or reagents used in the assay. Therefore, the same assay and reagents are recommended to be used to monitor factor IX activity over time.

The results of factor IX activity tests are lower if measured with chromogenic substrate assay (CSA) compared to OSA. In the clinical efficacy study with HEMGENIX, the post-dose factor IX activity measured with CSA returned lower values with the mean CSA to OSA factor IX activity ratio ranging from 0.41 to 0.55.

Monitor patients through appropriate clinical observations and laboratory tests for the development of inhibitors to factor IX after HEMGENIX administration. Perform an assay that detects factor IX inhibitors if bleeding is not controlled, or plasma factor IX activity levels decrease.

c. List potential drug-drug interactions if deemed clinically significant

The HEMGENIX full Prescribing Information does not provide information about interactions with other medicinal products.

10. COMPARISONS

N/A

Please see Important Safety Information on page 10 and accompanying full Prescribing Information for HEMGENIX.

HEMGENIX®
etranacogene dezaparvovec-drlb

Healthcare Systems

Important Safety Information

Warning and Precautions

Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. 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/Hepatocellular Carcinoma

Post-dose, monitor for elevated transaminase levels. Consider corticosteroid treatment should elevations occur. The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors for hepatocellular carcinogenicity, perform regular (eg, annual) abdominal ultrasound and alpha-fetoprotein testing following administration.

Immune-mediated neutralization of the AAV5 vector capsid

Preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired levels.

Monitoring Laboratory Tests

In addition to monitoring liver function, monitor for Factor IX activity and Factor IX inhibitors after administration.

Adverse Reactions

The most common adverse reactions (incidence ≥5%) were elevated ALT, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, nausea, malaise, and elevated AST.

Indication

HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

HEMGENIX is for single use intravenous infusion only.

Contraindications: None.

Please see accompanying full prescribing information for HEMGENIX.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. AHFS classification – drug assignments. AHFS Clinical Drug Information. Accessed January 9, 2024. https://ahfsdruginformation.com/ahfs-classification-drug-assignments/ **2.** BLA approval. US Food and Drug Administration. November 22, 2022. Accessed January 9, 2024. https://www.fda.gov/media/163466/download

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