CSL Behring

P&T summary

The first FDA-approved gene therapy for hemophilia B

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.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Healthcare Systems

HEMGENIX®
etranacogene dezaparvovec-drlb

Table of contents

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

HEMGENIX® etranacogene dezaparvovec-drlb

Impact of hemophilia B

Disease state overview

Hemophilia is a rare genetic bleeding disorder characterized by the inability of a person's blood to clot properly, resulting in excessive and prolonged bleeding from minor trauma, tooth extractions, or surgery, as well as easy bruising, or spontaneous bleeding in some cases.[1-3] Hemophilia A and B are the main variants of hemophilia; hemophilia B, the less common of the two,[2,3] occurs in 5 per 100,000 male births.[3,4]

Hemophilia B is caused by a defect in a gene encoding coagulation factor IX, which is expressed primarily in hepatocytes.[3,5] Hereditary genetics are not solely responsible for the disease state. Nearly one-third of all mutations are spontaneous.[3,6] The severity of hemophilia B is dependent on native coagulation factor activity; severe hemophilia B is characterized by frequent spontaneous and/or traumatic bleeding into joints, muscles, and internal organs, and can result in reduced life expectancy.[2,3,7]

Epidemiology of hemophilia B

The exact number of prevalent cases of hemophilia B in the United States is not known.[8] A 2020 study indicates that the condition is more prevalent than previously believed, with the rate of hemophilia B estimated at 3.7 per 100,000 in the male population (compared with 12 per 100,000 for hemophilia A). The incidence rate was estimated at 5.3 per 100,000 male births, or 1 case per 19,283 live male births.[9]

In terms of prevalence, 33,000 Americans have hemophilia.[8] Of those with hemophilia B, about 1600 are on prophylactic factor IX therapy, with approximately 800 adults who could be appropriate candidates for HEMGENIX® (etranacogene dezaparvovec-drlb). That translates to about 2 to 3 members per every 1-million-member healthcare plan.[10]

Hemophilia B symptoms vary depending on the severity of disease and level of factor IX activity.[3] The most common clinical manifestations of hemophilia B are frequent, recurring, and prolonged bleeding episodes that can be internal (such as bleeding into joints and muscles) or external (bleeding from minor cuts, dental procedures, or trauma).[2,11] Signs that are strongly suggestive of a hemophilia diagnosis include a history of easy bruising; "spontaneous" bleeding, particularly into the joints, muscles, and soft tissues; or excessive bleeding following trauma or surgery.[3]

Disease burden

Hemophilia B has an adverse impact on health-related quality of life and is associated with a substantial societal/humanistic burden.[12] The acute and chronic pain commonly experienced by patients can be debilitating, causing physical and functional impairment, reduced participation in recreational activities, psychological and emotional distress (manifested through depression and anxiety, for example), and impairment of overall health status.[13-15] Hemophilia B also has an impact on patients' interpersonal relationships, with pediatric patients facing bullying and adult patients reporting negative reactions from friends and colleagues.[15,16] In addition, the condition negatively affects patients' educational pursuits and work through its impact on mobility, trouble with concentrating, and the time required to attend treatment, especially for those who undergo routine factor IX prophylactic replacement therapy.[17]

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Impact of hemophilia B (cont'd)

Economic burden

The economic burden of hemophilia B has been driven largely by the cost of factor IX replacement therapy, which is substantial and accounts for more than 90% of the direct medical costs associated with the condition.[12,18] Hemophilia B is also associated with substantial use of non–factor IX treatment healthcare resources, such as physicians' office visits, outpatient visits, emergency department (ED) visits, and hospitalizations for bleeding. The use of factor IX replacement therapy and other healthcare resources is required for life, making these lifetime costs. The adult lifetime direct medical cost of hemophilia B per patient has been estimated at $21.0 million for standard half-life (SHL) factor IX prophylaxis, $22.9 million for extended half-life (EHL) factor IX prophylaxis, and $20.9 million for on-demand factor IX therapy (2019 cost values). The adult lifetime cost per patient from a societal perspective—combining direct medical and non-medical and indirect costs—has been estimated at approximately $21.1 million for SHL factor IX prophylaxis, $23.0 million for EHL factor IX prophylaxis, and $21.0 million for on-demand factor IX therapy.[18]

Patients with hemophilia B have been shown to incur total annual healthcare costs 25 times higher than matched controls ($201,635 vs $7879 per person; $P<0.001$ [2019 cost values]). Besides pharmacy costs, the leading drivers of cost for people with hemophilia B vs controls included excess inpatient admissions and ED, outpatient, and specialist visits.[18]

Treatment options

The standard of care for the treatment of hemophilia B—as set forth in the current World Federation of Hemophilia clinical guidelines for the management of the condition, which were published before the approval of gene therapy—is factor IX replacement via intravenous infusion of recombinant or plasma-derived factor IX concentrates.[3] The National Bleeding Disorders Foundation guidelines recommend recombinant over plasma-derived factor IX concentrates as the preferred option.[19] Factor IX replacement therapy may be provided under a prophylaxis (regular replacement) regimen, which requires routine and frequent infusions, or as on-demand (episodic) therapy, which is given to stop bleeding episodes when they occur. Nonetheless, the current guidelines and recommendations recognize gene therapy as an emerging therapy with the potential to provide better health outcomes and quality-of-life improvement compared with clotting factor concentrates, and to be considered as a treatment option for adult patients with severe disease.[3,19]

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Product introduction

HEMGENIX is an in vivo gene transfer therapy specifically designed to target hemophilia B

HEMGENIX consists of a non-replicating recombinant adeno-associated virus serotype 5 (AAV5) vector containing the highly active Padua variant of the F9 gene.

The non-replicating, non-pathogenic AAV5 vector was chosen because there is a lower prevalence of preexisting immunity (neutralizing antibodies) to it in the general population. AAV5 targets liver cells* and also has a serotype-specific tropism for hepatocytes, which are an ideal target for transduction as they are where factor IX is normally produced.

Factor IX-Padua has been shown to generate 5 to 10 times higher mean endogenous factor IX activity than the more common wild-type gene.[20] The factor IX-Padua gene is under the control of a liver-specific promoter.

*Based on animal studies.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX

Indications and usage

HEMGENIX is an AAV 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

Dosage and administration

For single-use intravenous infusion only

The recommended dose of HEMGENIX is 2×10^{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 (2×10^{13} gc/kg) divided by the amount of genome copies per mL of the HEMGENIX solution (1×10^{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 1×10^{13} gc/mL, and each vial contains an extractable volume of not less than 10 mL

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Dosage and administration (cont'd)

Preparation

The vials are for single dose only

Preparation of 0.9% normal saline infusion bags

1. Prior to dilution, spike the infusion bag(s) of 0.9% normal saline solution with applicable connector.
2. Connect a luer-lock syringe at the mixing adapter site of the applicable connector.
3. Withdraw the volume equal to the calculated HEMGENIX dose (in mL) from the 500 mL infusion bag(s) of 0.9% normal saline solution. The volume to be withdrawn and number of infusion bag(s) needed will vary based on the patient's body weight.

Example calculation for 72 kg patient

Patient body weight	Number of 500 mL 0.9% normal saline infusion bag(s) required	Volume of saline solution to withdraw
<120 kg	1	Equal to the total HEMGENIX dose (in mL) from 1 bag
≥120 kg	2	Equal to the total HEMGENIX dose (in mL). Remove half of the dose equivalent volume from each of the 2 bags

HEMGENIX injection to the 0.9% normal saline infusion bags

- Dilute HEMGENIX with 0.9% normal saline solution only prior to administration

4. Prior to dilution, inspect each of the HEMGENIX single-dose vials.
   - If particulates, cloudiness, or discoloration are visible, DO NOT use the vial(s)
5. Gently swirl the vials 3 times (about 10 seconds) to homogenize the HEMGENIX suspension.
   - To avoid foaming, DO NOT shake the HEMGENIX vial(s)
6. Remove the plastic flip-off cap from the vial(s) and disinfect the rubber stopper with a sterilizing agent (eg, sterile 70% isopropyl alcohol).
7. Withdraw HEMGENIX from each vial using a 20 G needle/vial adapter and syringe.
   - Use recommended 20 mL luer-lock or larger syringe that is suitable for volume measuring and a needle
   - DO NOT use filter needles during preparation of HEMGENIX
   - Use a new needle/vial adapter and syringe for each HEMGENIX vial
   - Dispose of the needle and syringe in an appropriate container
8. Slowly add the required HEMGENIX dose from the syringe(s) directly to the 0.9% normal saline solution in the infusion bag(s) (from step 3) to bring the total volume in each infusion bag back to 500 mL.
   - DO NOT add HEMGENIX into the airspace of the bag to avoid foaming throughout this process
9. Repeat steps 7 and 8 with additional needles/vial adapters and syringes to inject the total calculated HEMGENIX volume to the infusion bag(s) required for the patient dose.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Dosage and administration (cont'd)

Preparation (cont'd)

10. Gently invert the infusion bag(s) at least 3 times (about 10 seconds) to mix the solution and ensure even distribution of the diluted product.

- To avoid foaming, DO NOT shake the diluted HEMGENIX infusion bag(s)

11. Label the infusion bag(s).

12. Connect the infusion bag(s) to an infusion tube prefilled with sterile 0.9% normal saline solution to reduce the risk of spillage and/or aerosol formation.

13. Transport the diluted HEMGENIX infusion bag(s) in the transport container/bag protected from light to the administration site, avoiding any shaking or excessive agitation.

Administration

Required supplies and materials for administration

Winged intravenous needle or catheter set
Infusion pump
0.2 mcm in-line filter
Antiseptic skin preps
70% isopropyl alcohol wipes
Gauze and tape, or transparent dressing
Sharps disposal container
Virucidal agent to treat spill/spill kit

Administer HEMGENIX as a single-dose intravenous infusion through a peripheral venous catheter

1. Visually inspect diluted HEMGENIX prior to administration. The diluted HEMGENIX should be clear and colorless.

- DO NOT use if particulates, cloudiness, or discoloration are visible
- Use the diluted HEMGENIX within 24 hours after the dose preparation

2. Use an integrated (in-line) 0.2 mcm filter made out of polyether sulfone.

3. Subsequently, connect the prefilled intravenous infusion line/drip chamber to the main intravenous line, which has been primed with sterile 0.9% normal saline solution prior to use.

4. Infuse diluted HEMGENIX at a constant infusion rate of 500 mL/hour (8 mL/min).

- DO NOT administer HEMGENIX as an intravenous push or bolus
- DO NOT infuse the diluted HEMGENIX solution in the same intravenous line with any other products
- DO NOT use a central line or port

In the event of an infusion reaction during administration [see Warnings and Precautions (5.1) in the full Prescribing Information]:

- The rate of infusion may be reduced or stopped to manage the infusion reaction. If the infusion is stopped, re-start at a slower rate when the infusion reaction is resolved
- If the infusion rate needs to be reduced, or stopped and re-started, HEMGENIX should be infused within 24 hours after the dose preparation [see How Supplied/Storage and Handling (16.2) in the full Prescribing Information]

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Dosage and administration (cont'd)

Administration (cont'd)

5. After the entire content of the bag(s) is infused, flush the intravenous infusion line/drip chamber at the same infusion rate with 0.9% normal saline solution to ensure all HEMGENIX is delivered.
   - Treat spills of HEMGENIX with a virucidal agent with proven activity against non-enveloped viruses
   - Dispose of unused product and disposable materials that may have come in contact with HEMGENIX in accordance with local biosafety guidelines applicable for handling and disposal of the pharmaceutical waste

Monitoring post administration

Conduct the following tests after HEMGENIX administration [see Warnings and Precautions (5.2, 5.3, and 5.4) in the full Prescribing Information]:

- Perform regular liver enzyme testing to monitor for liver enzyme elevations, which may indicate immune-mediated hepatotoxicity
  - Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (transaminase) levels by testing weekly for 3 months following administration of HEMGENIX. Continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline
  - In the event of ALT increase to above normal limits or to twice the patient's baseline in the first 3 months post dose, consider implementing a course of corticosteroids. For patients with clinically relevant ALT increases who need corticosteroid treatment, administer the recommended starting dose of 60 mg/day of oral prednisolone or prednisone, with a subsequent taper in response to normalization of the ALT levels (see the table below)

Prednisolone treatment applied in clinical studies with HEMGENIX

Timeline	Prednisolone oral dose (mg/day)[a]
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance dose until ALT level returns to baseline level	20
Taper dose after ALT baseline level has been reached	Reduce daily dose by 5 mg/week

[a]Medications equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other products can be considered in case of prednisolone treatment failure or contraindication.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Dosage and administration (cont'd)

Administration (cont'd)

Monitoring post administration (cont'd)

In the clinical studies, the mean duration of corticosteroid use for elevated transaminases was 81.4 days (standard deviation [SD] 28.6) and ranged from 51 to 130 days [see Warnings and Precautions (5.2) in the full Prescribing Information].

- Monitor factor IX activity (eg, weekly for 3 months)
  - Monitor patients regularly for their factor IX activity, in particular when exogenous factor IX is administered. It may take several weeks before improved hemostatic control becomes apparent after HEMGENIX infusion; therefore, continued hemostatic support with exogenous human factor IX may be needed during the first weeks after HEMGENIX infusion [see Clinical Pharmacology (12.3) in the full Prescribing Information]
  - The use of different assays may impact the test results; therefore, use the same assay and reagents to monitor patients over time, if feasible [see Warnings and Precautions (5.5) in the full Prescribing Information]
  - Use of exogenous factor IX concentrates before and after HEMGENIX administration may impede assessment of endogenous, HEMGENIX-derived factor IX activity
- Perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (eg, annually) in patients with preexisting risk factors for hepatocellular carcinoma (eg, in patients with cirrhosis, advanced hepatic fibrosis, hepatitis B or C, nonalcoholic fatty liver disease [NAFLD], chronic alcohol consumption, nonalcoholic steatohepatitis [NASH], and advanced age)
- Monitor patients for human factor IX inhibitors. Post-dose inhibitor testing should be performed if bleeding is not controlled, or plasma factor IX activity levels decrease [see Warnings and Precautions (5.5) in the full Prescribing Information]

Dosage forms and strengths

HEMGENIX is a clear and colorless suspension for intravenous infusion.

HEMGENIX is provided in a kit containing 10 to 48 vials. 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.

Contraindications

None.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

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 [see Adverse Reactions (6) in the full Prescribing Information].

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 [see Dosage and Administration (2.1) in the full Prescribing Information].

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 the upper limit of normal (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) [see Adverse Reactions (6.1) in the full Prescribing Information].

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 [see Dosage and Administration (2.3) in the full Prescribing Information].

In case of increased ALT levels above ULN or double baseline levels, consider implementing a course of corticosteroid, along with human factor IX activity monitoring [see Dosage and Administration (2.3) in the full Prescribing Information].

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 with 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 [see Clinical Studies (14) in the full Prescribing Information].

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Warnings and precautions (cont'd)

Immune-mediated neutralization of the AAV5 vector capsid (cont'd)

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.

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 [see Clinical Studies (14) in the full Prescribing Information]. 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, NAFLD, chronic alcohol consumption, NASH, and advanced age) should receive abdominal ultrasound screenings and be monitored regularly (eg, annually) for AFP elevations in the 5 years following administration [see Dosage and Administration (2.3) in the full Prescribing Information].

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 with 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.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Adverse reactions

The most common adverse reactions (incidence ≥5%) reported in clinical studies were ALT elevations, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, malaise, and 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 with 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 serious adverse reactions were reported [see Clinical Studies (14) in the full Prescribing Information]. 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 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Adverse reactions (cont'd)

Clinical trials experience (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 13).

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

Five subjects had ALT elevations >2 to 3x 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 [see Clinical Studies (14) in the full Prescribing Information].

Immunogenicity

In clinical studies, sustained humoral immune response to infused AAV5 capsid was observed in all subjects following treatment with HEMGENIX. The neutralizing anti-AAV5 antibody levels raised above the upper limit of quantification by week 3 post administration and remained elevated, as measured at month 24 post dose. Re-administration of HEMGENIX in the presence of high anti-AAV5 antibody titer has not been evaluated. Currently, there is no validated neutralizing anti-AAV5 antibody assay.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Use in specific populations

Pregnancy

Risk summary

HEMGENIX is not intended for administration in 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

Risk summary

HEMGENIX is not intended for administration in women.

Females and males of reproductive potential

Risk summary

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 with subjects aged 18 to 65 years, and no dose adjustment was made [see Clinical Studies (14) in the full Prescribing Information].

Hepatic impairment

Limited clinical data in subjects with liver impairment indicate numerically lower factor IX activity as compared with subjects without hepatic impairment [see Clinical Pharmacology (12.3) in the full Prescribing Information]. 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 [see Clinical Pharmacology (12.3) in the full Prescribing Information]. 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 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Description

HEMGENIX (etranacogene dezaparvovec-drlb) is an adeno-associated viral vector–based gene therapy for intravenous infusion after dilution. HEMGENIX is a non-replicating recombinant AAV5 containing a codon-optimized DNA sequence of the gain-of-function Padua variant of human factor IX (variant R338L), under control of a liver-specific promoter 1 (LP-1).

HEMGENIX has a nominal concentration of 1×10^{13} gc/mL. Each vial contains an extractable volume of no less than 10 mL of HEMGENIX and 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 is a sterile, clear, and colorless suspension, and contains no preservative. After dilution, HEMGENIX should be a clear and colorless suspension.

Clinical pharmacology

Mechanism of action

HEMGENIX is an AAV5-based gene therapy 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.

Pharmacodynamics

Factor IX activity

The mean factor IX activity levels over time, as measured by one-stage (aPTT-based) assay, are summarized in the table below. Subjects achieved a mean (± SD) uncontaminated (ie, excluding measurements within 5 half-lives of factor IX replacement therapy) factor IX activity levels of 39% (± 18.7), 41.5% (± 21.7), 36.9% (± 21.4), and 36.7 (± 19.0) of normal, respectively, at 6, 12, 18, and 24 months. The time to onset of factor IX protein expression post dose was detectable by first uncontaminated measurement at week 3 in the clinical efficacy study (N=54) [see Clinical Studies (14) in the full Prescribing Information].

Summary of uncontaminated factor IX activity over time following administration of 2×10^{13} gc/kg of HEMGENIX (full analysis set[a]; one-stage [aPTT-based] assay)

	Factor IX activity in % (one-stage)		
	Subject number (n[b])	Median (min, max)	Mean (SD)
Week 3	43	23.7 (4.9, 56.7)	26.8 (12.7)
Month 3	51	33.8 (7.6, 91.0)	36.8 (18.2)
Month 6	51	37.3 (8.2, 97.1)	39.0 (18.7)
Month 12	50	39.9 (5.9, 113.0)	41.5 (21.7)
Month 18	50	33.6 (4.5, 122.9)	36.9 (21.4)
Month 24	50	33.9 (4.7, 99.2)	36.7 (19.0)

[a]Full analysis set includes all 54 subjects dosed.

[b]Uncontaminated factor IX activity values exclude measurements within 5 half-lives of factor IX replacement therapy. Contaminated and missing values are not shown here. Specifically, the number of subjects excluded for contamination with factor IX replacement therapy at week 3, month 3, month 6, month 12, month 18, and month 24 were 10, 3, 3, 3, 3, and 2, respectively.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Clinical pharmacology (cont'd)

Pharmacodynamics (cont'd)

Pharmacodynamics in specific populations

Age

Limited data (N=7) from the subgroup aged 60 to 75 years showed that the mean factor IX activity levels were approximately up to 2-fold higher in this subgroup compared with the subgroup aged 18 to <40 years (N=31), but comparable to the subgroup aged 40 to <60 years (N=15).

Hepatic impairment

In the clinical efficacy study, subjects with varying degrees of baseline liver pathology—specifically the degree of hepatic steatosis with the controlled attenuation parameter (CAP) score of ≥S2 (≥260 decibels/m; range: 262 to 400; n=12) vs <S2 (<260 decibels/m; range: 100 to 259; n=28) and missing score (n=14)—were compared [see Clinical Studies (14) in the full Prescribing Information]. The mean (± SD) uncontaminated factor IX activity for <S2 vs ≥S2 subgroups at months 6, 12, 18, and 24 post dose were 40.8 (± 20.1) vs 34.5 (± 13.7), 46.4 (± 24.1) vs 32.6 (± 18.6), 41.6 (± 25.7) vs 29.2 (± 13.7), and 40.2 (± 19.8) vs 28.4 (± 13.1), respectively. Subjects with advanced liver impairment and advanced fibrosis (elastography of, eg, ≥9 kPA, or suggestive of or equal to METAVIR Stage 3 disease), were not studied.

Renal impairment

In the clinical efficacy study, subjects with mild renal impairment (creatinine clearance [CLcr] = 60 to 89 mL/min defined by Cockcroft-Gault equation, n=7) had about 37% higher factor IX activity relative to those with normal renal function (CLcr ≥90 mL/min; n=45) following HEMGENIX administration. One subject with moderate renal impairment (CLcr = 30 to 59 mL/min) had similar factor IX activity as subjects with normal renal function. HEMGENIX was not studied in subjects with severe renal impairment (CLcr = 15 to 29 mL/min) or end-stage renal disease (CLcr <15 mL/min).

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Clinical pharmacology (cont'd)

Pharmacokinetics

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 (NHPs). 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 [see Nonclinical Toxicology (13.2) in the full Prescribing Information].

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 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Non-clinical toxicology

Non-clinical studies were initiated with a predecessor of HEMGENIX product, rAAV5 expressing the wild-type human coagulation factor IX (rAAV5-hFIX). HEMGENIX was developed by introducing a 2-nucleotide change in the transgene for hFIX, generating the naturally occurring Padua variant of factor IX (rAAV5-hFIX-Padua).

Carcinogenesis, mutagenesis, and impairment of fertility

No traditional non-clinical carcinogenicity or mutagenicity studies were conducted with HEMGENIX; such studies were not indicated. No adverse effects were observed in mating rates and fertility indices in healthy naïve female mice following mating with males that were administered the predecessor of HEMGENIX [see Use in Specific Populations (8.3) in the full Prescribing Information]. To evaluate vector integration, host genomic DNA was isolated from liver tissue obtained from healthy mice and NHPs following intravenous administration of the predecessor of HEMGENIX. For both species, the identified rAAV5-hFIX vector DNA sequences represented episomal forms that were not integrated into the host DNA. A low level of integrated rAAV5-hFIX DNA was distributed throughout the host genome with no predilection to specific integration sites, including in genes associated with malignant transformation in humans.

Animal toxicology and/or pharmacology

A pharmacology study was conducted in a murine model of hemophilia B (*B6.129P2-F9^{tm1Dws}*). Intravenous administration of the predecessor of HEMGENIX at dose levels ranging from 5×10^{11} to 2.3×10^{14} gc/kg resulted in dose-dependent increases in plasma hFIX protein levels, plasma hFIX clotting activity, and vector transduction in the liver at 4 weeks post dose. Intravenous administration of HEMGENIX resulted in a no-observed-adverse-effect-level of 5×10^{13} gc/kg (the maximum dose level administered) in healthy mice and 9×10^{13} gc/kg in NHPs. Vector biodistribution to the liver and hFIX protein levels in the plasma occurred in a dose-dependent manner in both species. Anti-hFIX antibodies developed in 5 out of 12 NHPs administered HEMGENIX, which correlated with a decline in circulating hFIX protein levels beginning at 13 weeks post dose. One out of 10 healthy mice administered 5×10^{13} gc/kg of HEMGENIX or the predecessor of HEMGENIX developed pulmonary thrombi at 13 weeks post dose. This dose level is 2.5-fold higher than the recommended dose level for HEMGENIX. Compared with concurrent controls, prolonged prothrombin time, decreased aPTT, and decreased heart rates were observed in NHPs administered 9×10^{13} gc/kg of HEMGENIX during the 26-week study. This dose level is 4.5-fold higher than the recommended dose level for HEMGENIX.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Clinical studies

The efficacy of HEMGENIX was evaluated in a prospective, open-label, single-dose, single-arm, 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 x 10^{13} gc/kg body weight of HEMGENIX and entered a follow-up period of 5 years. The study is ongoing.

The 54 subjects prospectively completed a lead-in period of at least 6 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 noninferiority 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% 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 noninferiority of ABR during months 7 to 18 compared with 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 to 534 (approximately 20 weeks).

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%)

[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 3 subjects were on continuous prophylaxis.
[d]Noninferiority 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 3 subjects receiving continuous prophylaxis during months 7 to 18.

After a single dose of HEMGENIX, increases in factor IX activity were observed [see Clinical Pharmacology (12.3) in the full Prescribing Information].

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

How supplied

HEMGENIX is supplied as a sterile, preservative-free, clear, and colorless suspension.

HEMGENIX has a nominal concentration of 1×10^{13} gc/mL.

HEMGENIX is provided as a customized kit to meet dosing requirements for each patient [see Dosage and Administration (2.1) in the full Prescribing Information], with each kit containing 10 to 48 single-use vials (National Drug Code [NDC] 0053-0099-01), each with an extractable volume of no less than 10 mL of HEMGENIX (see table on page 22). The total number of vials in each kit corresponds to the dosing requirement for the individual patient depending on the patient's body weight [see Dosage and Administration (2.1) in the full Prescribing Information]. The customized kit is accompanied by the patient's specific identifier number (lot) on the outer carton. Each HEMGENIX kit may contain different drug product lots.

Review of Prescribing Information for HEMGENIX (cont'd)

How supplied (cont'd)

HEMGENIX multi-vial kits

Total number of vials per kit	Patient body weight (kg)	Total volume per kit (mL)	NDC number
10	46-50	100	0053-0100-10
11	51-55	110	0053-0110-11
12	56-60	120	0053-0120-12
13	61-65	130	0053-0130-13
14	66-70	140	0053-0140-14
15	71-75	150	0053-0150-15
16	76-80	160	0053-0160-16
17	81-85	170	0053-0170-17
18	86-90	180	0053-0180-18
19	91-95	190	0053-0190-19
20	96-100	200	0053-0200-20
21	101-105	210	0053-0210-21
22	106-110	220	0053-0220-22
23	111-115	230	0053-0230-23
24	116-120	240	0053-0240-24
25	121-125	250	0053-0250-25
26	126-130	260	0053-0260-26
27	131-135	270	0053-0270-27
28	136-140	280	0053-0280-28
29	141-145	290	0053-0290-29
30	146-150	300	0053-0300-30
31	151-155	310	0053-0310-31
32	156-160	320	0053-0320-32
33	161-165	330	0053-0330-33
34	166-170	340	0053-0340-34
35	171-175	350	0053-0350-35
36	176-180	360	0053-0360-36
37	181-185	370	0053-0370-37
38	186-190	380	0053-0380-38
39	191-195	390	0053-0390-39
40	196-200	400	0053-0400-40
41	201-205	410	0053-0410-41
42	206-210	420	0053-0420-42
43	211-215	430	0053-0430-43
44	216-220	440	0053-0440-44
45	221-225	450	0053-0450-45
46	226-230	460	0053-0460-46
47	231-235	470	0053-0470-47
48	236-240	480	0053-0480-48

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Storage and handling

- 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

After dilution

- 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 [see Dosage and Administration (2.2) in the full Prescribing Information]

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Review of Prescribing Information for HEMGENIX (cont'd)

Patient counseling information

Inform patients that:

- Pre-infusion blood tests will be necessary to look for factor IX inhibitors. If these exist, the patient may not be a good candidate for HEMGENIX [see Dosage and Administration (2) in the full Prescribing Information]
- Prior to HEMGENIX treatment, a liver ultrasound and elastography will be performed. Patients found to have preexisting risk factors for hepatocellular carcinoma will be monitored annually in the 5 years following infusion [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Infusion reactions can occur. Patients will be monitored during and for at least 3 hours following administration. If a reaction occurs, the infusion rate may be slowed or interrupted, then re-started at a slower rate [see Warnings and Precautions (5.1) in the full Prescribing Information]
- HEMGENIX can elevate certain liver enzymes. Weekly blood tests will be required to monitor for this for 3 months after treatment. Corticosteroid treatment may be necessary if this occurs [see Warnings and Precautions (5.2) in the full Prescribing Information]
- If post-infusion bleeding is not controlled or if bleeding returns, then blood tests will be performed for factor IX activity and neutralizing factor IX inhibitors [see Warnings and Precautions (5.5) in the full Prescribing Information]
- Vector distribution in blood (within the body) and vector shedding in semen and other excreta and secreta can occur post infusion. It is not known how long this will continue. Patients should not donate blood, organs, tissues, or cells for transplantation [see Clinical Pharmacology (12.3) in the full Prescribing Information]

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For patent information: www.cslbehring.com/products/patents (in-licensed from uniQure).

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Distribution and administration

Distribution of HEMGENIX

HEMGENIX will be available directly to hemophilia treatment centers from CSL Behring or via select specialty pharmacies.

Administration of HEMGENIX

Administer HEMGENIX as a single-dose intravenous infusion through a peripheral venous catheter at a hemophilia treatment center or healthcare provider's office.

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

Important Safety Information and Indication

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.

Healthcare Systems

HEMGENIX®
etranacogene dezaparvovec-drlb

References: 1. Liras A, Segovia C, Gabán AS. Advanced therapies for the treatment of hemophilia: future perspectives. *Orphanet J Rare Dis.* 2012;7:97. doi:10.1186/1750-1172-7-97 **2.** Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica.* 2020;105(3):545-553. doi:10.3324/haematol.2019.232132 **3.** Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia.* 2020;26(suppl 6):1-158. doi:10.1111/hae.14046 **4.** Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med.* 2019;171(8):540-546. doi:10.7326/M19-1208 **5.** Tatsumi K, Ohashi K, Mukobata S, et al. Hepatocyte is a sole cell type responsible for the production of coagulation factor IX in vivo. *Cell Med.* 2012;3(1-3):25-31. doi:10.3727/215517912X639496 **6.** Hemophilia B. National Organization for Rare Disorders (NORD). Updated September 20, 2023. Accessed February 23, 2024. https://rarediseases.org/rare-diseases/hemophilia-b/ **7.** Learn more about hemophilia B. The Coalition for Hemophilia B. Accessed February 23, 2024. https://www.hemob.org/about-hemophilia-b **8.** Data and statistics on hemophilia B. Centers for Disease Control and Prevention. Updated July 12, 2023. Accessed February 23, 2024. https://www.cdc.gov/ncbddd/hemophilia/data.html **9.** Soucie JM, Miller CH, Dupervil B, Le B, Buckner TW. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia.* 2020;26(3):487-493. doi:10.1111/hae.13998 **10.** Adivo market analytics. Data on file. Available from CSL Behring as DOF ETZ-001. **11.** What is hemophilia? Centers for Disease Control and Prevention. Updated October 24, 2023. Accessed February 23, 2024. https://www.cdc.gov/ncbddd/hemophilia/facts.html **12.** Burke T, Asghar S, O'Hara J, Chuang M, Sawyer EK, Li N. Clinical, humanistic, and economic burden of severe haemophilia B in adults receiving factor IX prophylaxis: findings from the CHESS II real-world burden of illness study in Europe. *Orphanet J Rare Dis.* 2021;16(1):521. doi:10.1186/s13023-021-02152-1 **13.** Bauer KA. Current challenges in the management of hemophilia. *Am J Manag Care.* 2015;21(6)(suppl):S112-S122. **14.** Buckner TW, Witkop M, Guelcher C, et al. Impact of hemophilia B on quality of life in affected men, women, and caregivers—assessment of patient-reported outcomes in the B-HERO-S study. *Eur J Haematol.* 2018;100(6):592-602. doi:10.1111/ejh.13055 **15.** Cutter S, Molter D, Dunn S, et al. Impact of mild to severe hemophilia on education and work by US men, women, and caregivers of children with hemophilia B: the Bridging Hemophilia B Experiences, Results and Opportunities into Solutions (B-HERO-S) study. *Eur J Haematol.* 2017;98(suppl 86):18-24. doi:10.1111/ejh.12851 **16.** Cutter S, Guelcher C, Hunter S, Rotellini D, Dunn S, Cooper DL. Mild-severe hemophilia B impacts relationships of US adults and children with hemophilia B and their families: results from the B-HERO-S study. *Patient Relat Outcome Meas.* 2019;10:257-266. doi:10.2147/PROM.S214188 **17.** Buckner TW, Bocharova I, Hagan K, et al. Health care resource utilization and cost burden of hemophilia B in the United States. *Blood Adv.* 2021;5(7):1954-1962. doi:10.1182/bloodadvances.2020003424 **18.** Li N, Sawyer EK, Maruszczyk K, et al. Adult lifetime cost of hemophilia B management in the US: payer and societal perspectives from a decision analytic model. *J Med Econ.* 2021;24(1):363-372. doi:10.1080/13696998.2021.1891088 **19.** MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system. National Bleeding Disorders Foundation. August 20, 2023. Accessed February 23, 2024. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-280-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system **20.** Simioni P, Tormene D, Tognin G, et al. X-linked thrombophilia with a mutant factor IX (factor IX Padua). *N Engl J Med.* 2009;361(17):1671-1675. doi:10.1056/NEJMoa0904377

Please see Important Safety Information on page 26 and accompanying full Prescribing Information for HEMGENIX.

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