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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use HEMGENIX safely and effectively. See full prescribing information for HEMGENIX.**

**HEMGENIX (etranacogene dezaparvovec-drlb) suspension, for intravenous infusion**
**Initial U.S. Approval: 2022**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Dosage and Administration (2.3) | 04/2026 |
| Warnings and Precautions (5) | 04/2026 |

**----------INDICATIONS AND USAGE----------**

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.

**----------DOSAGE AND ADMINISTRATION----------**

**For single-use intravenous infusion only. (2)**

- Perform baseline testing to select patients, including testing for Factor IX inhibitor presence and liver health tests. (2.1)
- The recommended dose of HEMGENIX is 2 x $10^{13}$ genome copies (gc) per kg of body weight. (2.1)
- 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). (2.1)

**----------DOSAGE FORMS AND STRENGTHS----------**

HEMGENIX is a suspension for intravenous infusion. (3)
HEMGENIX is provided in kits containing 10 to 48 single-use vials, each kit constituting a dosage unit based on the patient's body weight. (3)
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. (3)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------WARNINGS AND 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. (2.3, 5.1)
- Hepatotoxicity: Monitor transaminase levels once per week for 3 months and thereafter monthly up to 1 year after HEMGENIX administration to mitigate the risk of potential hepatotoxicity. Consider corticosteroid treatment should elevations occur and as clinically indicated (5.2)
- Hepatocellular carcinogenicity: For patients with preexisting risk factors consider liver ultrasound and alpha-fetoprotein testing following administration. (5.4)
- Monitoring Laboratory tests: Monitor for Factor IX activity and Factor IX inhibitors. (5.5)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions (incidence ≥5%) were elevated ALT, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, malaise and elevated AST. (6)

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

**----------USE IN SPECIFIC POPULATIONS----------**

No dose adjustment is required in geriatric, hepatic, or renal impaired patients. (8.5, 8.6, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 04/2026**

**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

HEMGENIX is indicated for 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Critical Administration-related Information:

**For single-use intravenous infusion only.**

For patient selection:

- Perform Factor IX inhibitor titer testing. Do not administer HEMGENIX for patients with positive FIX inhibitors or a prior history for FIX inhibitors.
- Perform liver health assessments, including: Enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin)], hepatic ultrasound and elastography. In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consider a consultation with hepatologist to assess eligibility for HEMGENIX.
- Perform laboratory tests to evaluate active hepatitis B and C. Postpone HEMGENIX treatment until patient does not have active hepatitis B or C infection as active infection may reduce the efficacy of HEMGENIX and/or increase the risk of adverse reactions *[see Warnings and Precautions (5.2)]*.

### 2.2 Dose

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) *[see Dosage and Administration (2.2)]*. Calculate the dose as follows:

HEMGENIX dose (in mL) = patient body weight (in kilogram) 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 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:

HEMGENIX dose (in ML) = 72 x 2 = 144 mL
Number of HEMGENIX vials needed = 144 (mL) / 10(mL per vial) = 14.4 vials = 15 Vials (rounded up)

HEMGENIX can be administered only once.

### 2.3 Preparation

**The vials are for single-dose only.**

General precautions

- Prepare HEMGENIX using sterile technique under aseptic conditions, proper engineering controls (e.g., biological safety cabinet or isolator) and according to institutional policies.
- Do not expose HEMGENIX to the light of an ultraviolet radiation disinfection lamp.
- Confirm that the patient's identity matches with the patient-specific identifier number on the outer carton.
- Verify the required dose of HEMGENIX based on the patient's body weight.
- Confirm that the carton contains sufficient number of vials to prepare the diluted HEMGENIX patient-specific infusion bag.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Required supplies and materials:

- Normal saline infusion bag(s)* of 500 mL (1 to 2 bags based on patient's body weight)
- Labels** for the infusion bag(s) of 500 mL
- IV Infusion line/drip chamber* primed with 0.9% normal saline
- Infusion bag connector(s)
- 20 mL or larger Luer-lock syringes*
- 20 G Needles* or vial adaptors*
- 70% isopropyl alcohol
- Sharps disposal container

The following Table shows the supplies and materials compatible with HEMGENIX:

**Table 1. Supplies and Materials compatible with HEMGENIX**

| Component* | Material of Construction |
|---|---|
| Normal saline infusion bag (0.9% normal saline) | PE/PP copolymer (PVC-free) (Stability after dilution was established using PE/PP copolymer, PVC-free infusion bags with 0.9% normal saline.) |
| 20 G Needle | Stainless Steel |
| Vial adapter | PP, Silicone; PP, stainless; MABS, acrylic silicone; ABS |
| Luer-lock syringe | PP, Silicone |
| IV Infusion line/drip chamber | PVC/TOTM, PP/styrene-ethylene-butylene-styrene |

MABS = Methyl methacrylate acrylonitrile butadiene styrene; PE = Polyethylene; PP = Polypropylene; PVC = Polyvinyl chloride; TOTM = Trioctyltrimellitate, Acrylonitrile butadiene styrene (ABS)

**Information to be included on the infusion bag label:
- Product name: Diluted Hemgenix
- Patient identifier
- Expiration date/time (24 h from the vial removal from refrigerator)
- Storage condition: Room Temperature [15-25 °C (59-77 °F] protected from light.
- Contains genetically modified organisms
- Number of infusion bag: 1 of 2 bags / 2 of 2 bags

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 body weight.

**Table 2. Volume of saline solution to be withdrawn based on patient body weight**

| **Patient body weight** | **Number of 500 mL 0.9% normal saline infusion bag(s) required** | **Volume of saline solution to withdraw** |
|---|---|---|
| Less than 120 kg body weight | One | Equal to the total HEMGENIX dose (in mL) from one bag |
| Equal to or more than 120 kg body weight | Two | Equal to the total HEMGENIX dose (in mL). Remove half of the dose equivalent volume from each of the two 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 is 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 vials and disinfect the rubber stopper with a sterilizing agent (for example 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 adaptors and syringes to inject the total calculated HEMGENIX volume to the infusion bag(s) required for the patient dose.

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 pre-filled 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.

### 2.4 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

The following Table shows the supplies and materials compatible for infusion of HEMGENIX

**Table 3. Supplies and materials compatible for infusion of HEMGENIX**

| Component* | Material of Construction |
|---|---|
| Winged IV needle or catheter set | PVC/TOTM, MABS |
| 0.2 mcm in-line filter | PES |
| Catheter | PVC/DEHT, Stainless steel |

DEHP = Di(2-ethylhexyl)phthalate; DEHT = Di(2-ethylhexyl)terephthalate; MABS = Methyl methacrylate acrylonitrile butadiene styrene; PES = Polyether sulfone; PVC = Polyvinyl chloride

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 *[see How supplied/Storage and Handling (16.2)]*.

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

3. Subsequently, connect the pre-filled IV 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.

    - DO NOT infuse HEMGENIX faster than 500 mL/hour

In the event of an infusion reaction during administration *[see Warnings and Precautions (5.1)]*:

- The rate of infusion may be reduced or stopped, to manage the infusion reaction.
  If the infusion is stopped, restart at a slower rate when the infusion reaction is resolved.
- If the infusion rate needs to be reduced, or stopped and restarted, HEMGENIX should be infused within 24 hours after the dose preparation *[see How supplied/Storage and handling (16.2)]*.

5. After the entire content of the bag(s) is infused, flush the IV 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.

For post administration monitoring *[see Warnings and Precautions (5.2, 5.4, 5.5), Clinical Trial Experience (6.1)]*

## 3 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.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity and Infusion-Related Reactions

Moderate to severe hypersensitivity and infusion-related reactions have occurred with HEMGENIX treatment *[see Adverse Reactions (6)]*. Anaphylaxis may occur with

HEMGENIX treatment. Symptoms may include chest tightness, headaches, abdominal pain, lightheadedness, flu-like symptoms, shivering, flushing, rash, and hypertension.

Monitor patients for signs or symptoms of hypersensitivity and infusion-related 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 event of hypersensitivity or infusion reaction during administration, the infusion may be slowed or stopped. If the infusion is stopped, restart at a slower rate when the symptoms have resolved. Consider treatment with a corticosteroid or antihistamine for management of the reaction *[see Clinical Trial Experience (6.1)]*.

**5.2 Hepatotoxicity**

Hepatotoxicity with elevated liver transaminase has occurred after HEMGENIX treatment due to intravenous administration of a liver-directed AAV vector *[see Adverse Reactions (6)]*. Transaminitis may be immune mediated and reduce the therapeutic efficacy of the AAV-vector based gene therapy.

Monitor ALT levels by testing weekly for 3 months and thereafter monthly for up to 1 year following administration of HEMGENIX to mitigate risk of immune-mediated hepatotoxicity and potential decrease in Factor IX activity. Investigate alternative causes of ALT and other transaminase elevations.

In case of increased ALT levels above the upper limit of normal or double baseline levels consider a course of corticosteroid, with a subsequent taper, along with Factor IX activity monitoring Monitor ALT until it returns to baseline, or until after completion of corticosteroid treatment or as clinically indicated. *[see Clinical Trial Experience (6.1)]*

**5.3 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. Immune-mediated neutralizing antibodies to AAV5 vector capsid occurred after treatment with HEMGENIX.

Following treatment with HEMGENIX all patients developed neutralizing anti-AAV5 antibodies.

**5.4 Hepatocellular carcinogenicity**

Hepatocellular carcinoma related to HEMGENIX has not been observed. Hepatocellular carcinoma may develop after treatment with HEMGENIX due to the integration of liver-targeting AAV vector DNA into the genome.

Monitor for hepatocellular carcinomas for five years following administration of HEMGENIX in patients at high risk for hepatocellular carcinoma through abdominal ultrasound screenings and serum alfa-fetoprotein (AFP) levels. *[see Clinical Trials Experience (6.1)]*.

### 5.5 Monitoring Laboratory Tests

Monitor plasma Factor IX activity (e.g., weekly for 3 months) by performing either activated partial thromboplastin time (aPTT)-based one-stage clotting assay (OSA) or chromogenic substrate assay (CSA). Factor IX activity results may be lower with CSA compared to OSA [*see Pharmacodynamics (12.2)*]. Monitor Factor IX activity using same assay. Use same reagents and reference standards for OSA and CSA to minimize inconsistencies in Factor IX activity.

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)]*. Use of exogenous Factor IX concentrates before and after HEMGENIX administration may impede assessment of endogenous, HEMGENIX-derived Factor IX activity.

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.

## 6 ADVERSE REACTIONS

### 6.1 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 two clinical studies (study 1 enrolled 3 patients and study 2 enrolled 54 patients). Both studies enrolled adult male patients with moderately severe or severe Hemophilia B (N = 57), who received a single intravenous dose of $2 \times 10^{13}$ gc/kg body weight of HEMGENIX. Three patients in study 1 and 50 of 54 patients from study 2 completed the study-specific 5-year follow-up period.

No serious adverse reactions were reported *[see Clinical Studies (14)]*. The most common adverse reactions observed in ≥5% of patients post-dose are listed in Table 4:

**Table 4. Adverse Reactions (Incidence ≥5%) Following Treatment with HEMGENIX Months 0-24**

| Adverse Reactions ≥5% | Patients (%) (N = 57) |
|---|---|
| Alanine aminotransferase increased | 23 (40%) |
| Headache | 10 (18%) |
| Blood creatine kinase increased | 24 (42%) |
| Flu-like symptoms | 8 (14%) |
| Infusion-related reactions* (see below) | 19* (33%) |
| Hypersensitivity | 2** (4%) |
| Fatigue | 7 (12%) |
| Aspartate aminotransferase increased | 24 (42%) |
| Nausea | 4 (7%) |
| Malaise | 7 (12%) |

*Infusion-related reaction: Symptoms occurred during and after infusion in 7 and 12 patients, respectively. Infusions were temporarily interrupted and resumed at a slower infusion rate after treatment with antihistamines and/or corticosteroids in 3 patients. Eleven patients recovered on the day of or day after infusion, and eight patients recovered within 8 days after infusion.

** Hypersensitivity reactions occurred within 10-12 minutes following initiation of HEMGENIX infusion. One patient needed supportive therapy and received only 10% of the intended HEMGENIX dose. The other patient did not receive supportive therapy and received the full HEMGENIX dose. Symptoms resolved in both patients on the same day.

Hepatic transaminases were monitored weekly for 3 months and then monthly thereafter till 1 year following HEMGENIX administration. There were 23 patients who had asymptomatic elevated ALT values > ULN during the first 2-years post-administration (median ALT = 65, range = 41-275). Seventeen of 23 patients had elevated ALT levels in the first 4 months after HEMGENIX administration. The remaining 6 patients had elevated ALT levels between months 4-24. ALT levels were elevated in 9 patients at the end of the 2-year follow-up period. Four patients had ALT elevations >2-3x ULN (range = 89 IU/L – 130 IU/L), one patient had an ALT elevation > 3-5x ULN (range = 157 IU/L – 214 IU/L) and one patient had an ALT elevation > 5x ULN (275 IU/L). The patient who had the ALT elevation >5x

ULN occurred 3 weeks after HEMGENIX administration. The remaining seventeen patients had ALT elevation ≤2x ULN.

Nine patients with ALT elevations received a tapered course of corticosteroids based on a schedule as outlined in Table 5. The median (range) time to corticosteroid initiation was 41 (22-61) days. The median (range) duration of corticosteroid treatment for the elevated ALT was 73 (51-130) days. Fourteen patients had elevated ALT levels and were not treated with corticosteroids.

**Table 5. Prednisolone Treatment Applied in Clinical Studies With HEMGENIX:**

| **Timeline** | **[%],[$]Prednisolone Oral Dose (mg/day)** |
|---|---|
| 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 |

[%] 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.[$] Corticosteroid taper may be individualized based on trend of ALT decline, Factor IX activity, the patient's medical condition, corticosteroid tolerance, and adverse reactions to corticosteroid therapy.

Between 2 and 5 years after treatment, fourteen patients who had asymptomatic elevations in ALT above ULN after treatment (median ALT = 72, range = 42-65) and were not treated with corticosteroids during that period. Of the 14 patients, 6 patients had elevated ALT > ULN prior to year 2. At the end of the 5-year follow-up period, 6 patients had ALT values > ULN (median = 63, range = 49-119). Two of the 6 patients had alternative causes explaining their ALT elevation. Two patients treated with corticosteroids in the first year of follow-up, already had ALT values > ULN prior to treatment and continued to have ALT elevations through the 5-year follow up.

Other clinically significant adverse reactions include hepatocellular carcinoma in one patient with preexisting risk factors for developing hepatic cancer (history of hepatitis B and hepatitis C infections, and alcohol use), in whom relatedness was assessed as not likely related to HEMGENIX treatment based on vector integration site analyses and whole genome sequencing.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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 United States 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.

### 8.2 Lactation

Risk Summary

HEMGENIX is not intended for administration in women.

### 8.3 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.

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

The clinical studies included a total of 6 geriatric patients 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 patients compared to patients aged 18 to 65 years, and no dose adjustment was made *[see Clinical Studies (14)]*.

### 8.6 Hepatic Impairment

Limited clinical data in patients with liver impairment indicate numerically lower FIX activity as compared to patients without hepatic impairment *[see Clinical Pharmacology (12.3)]*. In the clinical studies, no dose adjustment was made in patients with hepatic pathologies. The safety and efficacy in patients with advanced hepatic impairment, including cirrhosis, advanced liver fibrosis, or uncontrolled hepatitis B and C, have not been studied.

### 8.7 Renal Impairment

Limited clinical data are available in patients with mild and moderate renal impairment *[see Clinical Pharmacology (12.3)]*. In the clinical studies, no dose adjustment was made in these patients. The

safety and efficacy in patients with severe renal impairment and end-stage renal disease have not been studied.

## 11 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 promotor 1 (LP1).

HEMGENIX has a nominal concentration of 1 x $10^{13}$ 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 sterile, clear and colorless suspension, and contains no preservative. After dilution, HEMGENIX should be clear and colorless suspension.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism 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 (hFIX-Padua). Single intravenous infusion of HEMGENIX results in cell transduction and increase in circulating Factor IX activity in patients with Hemophilia B.

### 12.2 Pharmacodynamics

Factor IX activity

The mean Factor IX activity levels over time, as measured by one-stage [activated Partial Thromboplastin Time (aPTT)-based] assay are summarized in Table 6. Patients achieved a mean (± SD) uncontaminated (i.e., excluding measurements within five half-lives of Factor IX replacement therapy) Factor IX activity levels of 39% (± 18.7), 41.5% (± 21.7), 36.9% (± 21.4), 36.7% (± 19.0), and 36.1% (± 15.7) of normal, respectively, at 6, 12, 18, 24, and 60 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)]*.

**Table 6. Summary of Uncontaminated Factor IX Activity Over Time Following Administration of 2 x $10^{13}$ gc/kg of HEMGENIX [FAS; One-Stage (aPTT-Based) Assay]**

| | Factor IX Activity in % (One-stage) | | |
|---|---|---|---|
| | **Subject Number (*n)** | **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) |
| Month 36 | 48 | 36.0 (4.8, 80.3) | 38.6 (17.8) |
| Month 48 | 47 | 34.6 (4.7, 80.1) | 37.4 (16.7) |
| Month 60 | 48 | 35.5 (5.5, 74.5) | 36.1 (15.7) |

Abbreviations: SD = Standard Deviation; FAS = Full Analysis Set including all 54 patients dosed; Min = Minimum; Max = Maximum. Uncontaminated Factor IX activity values exclude measurements within five half-lives of Factor IX replacement therapy.

*Contaminated and missing values are not shown here. Specifically, the number of patients excluded for contamination with Factor IX replacement therapy at Week 3, Month 3, Month 6, Month 12, Month 18, Month 24, Month 36, Month 48, and Month 60 were 10, 3, 3, 3, 3, 2, 2, 3, 1, respectively.

In the clinical efficacy study with HEMGENIX, the post-dose Factor IX activity measured with chromogenic substrate assay (CSA) returned lower values with the mean CSA to OSA Factor IX activity ratio ranging from 0.41 to 0.55.

Pharmacodynamics in specific populations

*Age*

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

*Hepatic Impairment*

In the clinical efficacy study, patients with varying degree 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) versus <S2 (<260 decibels/m; range: 100 to 259; n = 28;) and missing score (n = 14) were compared *[see Clinical Studies (14)]*. The mean (± SD) uncontaminated Factor IX activity for <S2 versus ≥S2 subgroups at Months 6, 12, 18, and 24 post dose were 40.8 (±20.1) versus 34.5 (±13.7), 46.4 (±24.1) versus 32.6 (±18.6), 41.6 (±25.7) versus 29.2 (±13.7), and 40.2 (±19.8) versus 28.4 (±13.1), respectively.

Patients with advanced liver impairment and advanced fibrosis (elastography of e.g., ≥9 kPA, or suggestive of or equal to METAVIR Stage 3 disease), were not studied.

*Renal Impairment*

In the clinical efficacy study, patients 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 patients with normal renal function.

HEMGENIX was not studied in patients with severe renal impairment (CLcr = 15 to 29 mL/min) or end-stage renal disease (CLcr< 15 mL/min).

### 12.3 Pharmacokinetics

Vector Biodistribution (within the body) and Vector Shedding (excretion/secretion)

*Nonclinical 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)]*.

*Clinical data*

Following administration of the predecessor of HEMGENIX at doses of 5 $x10^{12}$ (N = 5) and 2 x $10^{13}$ gc/kg (N = 5) in a clinical study, vector shedding was assessed in blood, saliva, nasal secretions, semen, urine, and feces. Clearance of vector DNA as confirmed by ≥3 consecutive measurements below limit of detection (LOD), using a quantitative PCR assay for vector DNA detection, was achieved in all patients at both dose levels from all the matrices except for semen, where clearance was achieved in 9/10 patients. 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 vector shedding in blood and semen following HEMGENIX administration was characterized in 2 clinical studies.

In an initial clinical study (N = 3), clearance of vector DNA from semen and blood (i.e., confirmed with ≥3 consecutive measurements below LOD of vector DNA) was achieved in 2/3 patients, and in all patients, respectively, 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 consecutive measurements below LOD of vector DNA.

In the clinical efficacy study (N = 54), a total of 56% (30/54) of patients achieved absence of vector DNA from blood and 69% (37/54) from semen by Month 24, as per the definition. Nine patients for semen and 5 patients for blood did not return the required number of

samples to assess the shedding status as per the definition of ≥3 consecutive 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 ) patients were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post-administration. At Month 60, clearance of vector DNA, as per the definition and accounting for missing samples, was confirmed in 90.7% (49/54) of patients in blood and in 83.3% (45/54) of patients in semen.

### 12.6 Immunogenicity

In the clinical efficacy study (N=54), sustained humoral immune response to infused AAV5 capsid was observed in all patients 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 60 post-dose. Re-administration of HEMGENIX in the presence of high anti-AAV5 antibody titer has not been evaluated.

## 13 NONCLINICAL TOXICOLOGY

Nonclinical 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).

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No traditional nonclinical 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)]*. 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.

### 13.2 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 $5x10^{11}$ to $2.3x10^{14}$ 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 x $10^{13}$ gc/kg (the maximum dose level administered) in healthy mice and 9 x $10^{13}$ 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 x $10^{13}$ 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 to concurrent controls, prolonged prothrombin time, decreased activated partial thromboplastin time and decreased heart rates were observed in NHPs administered 9 x $10^{13}$ gc/kg of HEMGENIX during the 26-week study. This dose level is 4.5-fold higher than the recommended dose level for HEMGENIX.

## 14 CLINICAL STUDIES

The efficacy of HEMGENIX was evaluated in a prospective, open-label, single-dose, single-arm, multi-national study (NCT03569891; N = 54). The study enrolled adult male patients 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

The 54 patients prospectively completed a lead-in period of at least six months with the intent to receive standard of care regular Factor IX prophylaxis. These 54 patients then received the indicated single intravenous dose of HEMGENIX. Patients were then followed up weekly until Month 3, monthly until Month 12, and then at 6-month intervals until Year 5 (Month 60). Of the 54 patients, 53 patients completed at least 24 months of follow-up and 50 patients completed 60 months of efficacy follow-up.

The primary efficacy evaluation was non-inferiority in annualized bleeding rate (ABR) during Months 7 to 18 after HEMGENIX treatment compared with ABR during the lead-in period as described in Table 7. All bleeding episodes, regardless of investigator assessment, were counted. Patients were allowed to continue prophylaxis during Months 0 to 6. 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.

**Table 7. 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 |

| | Lead-in Period[a] | Months 7 to 18[b] after HEMGENIX treatment |
|---|---|---|
| Mean Adjusted ABR (95% CI)[d] | 4.1 (3.2, 5.4) | 1.9 (1.0, 3.4) |
| Patients with Bleeds | 40 (74%) | 20 (37%) |
| Patients 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 patients 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 patients 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 patients 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 any patients receiving continuous prophylaxis during Months 7 to 18.

Four patients had regular or intermittent prophylaxis following HEMGENIX administration and are described below.

An unvalidated clinical trial assay was utilized to assess preexisting neutralizing anti-AAV5 antibodies. There were 21 patients with pre-treatment positive AAV5 antibody titers that ranged between 1:8.5-3212. Patients with detectable preexisting neutralizing anti-AAV5 antibodies up to titers of 1:678 showed mean Factor IX activity that was numerically lower compared to patients without detectable preexisting neutralizing anti-AAV5 antibodies. One patient with anti-AAV5 antibodies (1:3212) did not stop regular prophylaxis after HEMGENIX treatment due to lack of response.

One patient who received a partial dose administration continued regular prophylaxis. One patient resumed FIX prophylaxis beginning day 874. An additional patient received prophylaxis intermittently from Days 396-1825.

The adjusted ABR for months 7 to 60 after HEMGENIX treatment was 1.9 (95% CI: 1.0, 3.7).

Four patients did not complete the 5-year follow-up period: 2 patients due to treatment-unrelated death, 1 subject due to receiving a treatment-unrelated liver transplantation and 1 subject due to withdrawal of consent. Another subject received around 10% of the intended

dose of HEMGENIX due to an infusion-related hypersensitivity reaction but continued through to the study end and was included in the efficacy analysis.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

HEMGENIX is supplied as sterile, preservative-free, clear, and colorless suspension. HEMGENIX has a nominal concentration of $1 \times 10^{13}$ gc/mL.

HEMGENIX is provided as a customized kit to meet dosing requirements for each patient *[see Dosage and Administration (2.1)*], with each kit containing 10 (ten) to 48 (forty-eight) single-use vials (NDC 0053-0099-01), each with an extractable volume of no less than 10 mL of HEMGENIX (see5). The total number of vials in each kit corresponds to the dosing requirement for the individual patient depending on the patient`s body weight [s*ee Dosage and Administration (2.1)]*. The customized kit is accompanied with patient`s specific identifier number (Lot) on the outer carton. Each HEMGENIX kit may contain different drug product lots.

Kit sizes and National Drug Codes (NDC) are provided in Table 8:

**Table 8. 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 |

| Total Number of Vials per Kit | Patient Body Weight (kg) | Total Volume per Kit (mL) | NDC Number |
|---|---|---|---|
| 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 |

### 16.2 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)]*.

## 17 PATIENT COUNSELING INFORMATION

Inform patients that:

• Pre-infusion blood tests will be necessary to look for Factor IX inhibitors. If these exist, the patient is not a candidate for HEMGENIX *[see Dosage and Administration (2)]*.

• Prior to HEMGENIX treatment, a liver ultrasound and elastography will be performed. Patients found to have pre-existing risk factors for hepatocellular carcinoma will be monitored annually in the 5 years following infusion *[see Warnings and Precautions (5.4)]*.

• Infusion-related and allergic 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 started at a slower rate *[see Warnings and Precautions (5.1)]*.

• 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)]*.

• 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)]*.

• 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 Pharmacokinetics (12.3)]*.

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