ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Hemgenix 1 x 10^{13} genome copies/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Etranacogene dezaparvovec is a gene therapy medicinal product that expresses the human coagulation Factor IX. It is a non-replicating, recombinant adeno-associated virus serotype 5 (AAV5) based vector containing a codon-optimised cDNA of the human coagulation Factor IX variant R338L (FIX-Padua) gene under the control of a liver-specific promoter (LP1). Etranacogene dezaparvovec is produced in insect cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each mL of etranacogene dezaparvovec contains 1 x 10^{13} genome copies (gc).

Each vial contains an extractable volume of 10 mL of concentrate for solution for infusion, containing a total of 1 x 10^{14} genome copies.

The total number of vials in each pack corresponds to the dosing requirement for the individual patient, depending on the patient`s body weight (see sections 4.2 and 6.5).

Excipient with known effect

This medicinal product contains 35.2 mg sodium per vial (3.52 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hemgenix is indicated for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of Haemophilia and/or bleeding disorders. This medicinal product should be administered in a setting where personnel and equipment are immediately available to treat infusion related reactions (see sections 4.4 and 4.8).

Hemgenix should only be administered to patients who have demonstrated absence of Factor IX inhibitors. In case of a positive test result for human Factor IX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive Hemgenix.

In addition, before administration of Hemgenix, baseline testing of liver health and assessment of preexisting neutralising anti-AAV5 antibody titre should be performed; see section 4.4.

Posology

The recommended dose of Hemgenix is a single dose of 2×10^{13} gc/kg body weight corresponding to 2 mL/kg body weight, administered as an intravenous infusion after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection (see section 4.2 below and section 6.6).

Hemgenix can be administered only once.

Discontinuation of prophylaxis with exogenous human Factor IX
The onset of effect from etranacogene dezaparvovec treatment may occur within several weeks post-dose (see section 5.1). Therefore, haemostatic support with exogenous human Factor IX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient Factor IX coverage for the initial days post-treatment. Monitoring of the Factor IX activity (e.g. weekly for 3 months) is recommended post-dose to follow the patient`s response to etranacogene dezaparvovec.

When using an in vitro activated partial thromboplastin time (aPTT)-based one-stage clotting assay for determining Factor IX activity in patients' blood samples, 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 (see section 4.4). Therefore the same assay and reagents are recommended to be used to monitor Factor IX activity over time.

In case increased plasma Factor IX activity levels are not achieved, decrease, or bleeding is not controlled or returns, post-dose testing for Factor IX inhibitors is recommended along with Factor IX activity testing.

Special populations

Elderly population
No dose adjustments are recommended in elderly patients. Limited data are available in patients aged 65 years and older (see section 5.1).

Renal impairment
No dose adjustments are recommended in patients with any level of renal impairment.

The safety and efficacy of etranacogene dezaparvovec in patients with severe renal impairment and end-stage renal disease have not been studied (see section 5.2).

Hepatic impairment
No dose adjustments are recommended in patients with hepatic disorders (see sections 4.3 and 5.2).

The safety and efficacy of etranacogene dezaparvovec in patients with severe hepatic impairment have not been studied. Etranacogene dezaparvovec is contraindicated in patients with acute or uncontrolled chronic hepatic infections, or in patients with known advanced liver fibrosis, or cirrhosis (see section 4.3). This medicinal product is not recommended for use in patients with other significant hepatic disorders (see sections 4.4 and 5.2).

Patient with HIV

No dose adjustments are recommended in HIV-positive patients. Limited data are available in patients with controlled HIV infection.

Paediatric population
The safety and efficacy of etranacogene dezaparvovec in children aged 0 to 18 years have not been studied. No data are available.

Method of administration

Hemgenix is administered as a single-dose intravenous infusion after dilution of the required dose with sodium chloride 9 mg/mL (0.9%) solution for infusion. Etranacogene dezaparvovec must not be administered as an intravenous push or bolus.

For instructions on dilution of the product prior to administration, see section 6.6.

Infusion rate
The diluted product should be administered at a constant infusion rate of 500 mL/hour (8 mL/min).
- In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped to ensure patient tolerability. If the infusion is stopped, it may be restarted at a slower rate when the infusion reaction is resolved (see section 4.4).
- If the infusion rate needs to be reduced, or the infusion stopped and restarted, the etranacogene dezaparvovec solution should be infused within the shelf life of diluted etranacogene dezaparvovec, i.e. within 24 hours after the dose preparation (see section 6.3).

For detailed instructions on preparation, handling, measures to take in case of accidental exposure and disposal of Hemgenix, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Active infections, either acute or uncontrolled chronic.

- Patients with known advanced hepatic fibrosis, or cirrhosis (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Initiation of treatment with Hemgenix

Patients with pre-existing antibodies to the AAV5 vector capsid
Prior to the treatment with Hemgenix patients should be assessed for the titre of preexisting neutralising anti-AAV5 antibodies.

Preexisting neutralising anti-AAV antibodies above a titre of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of Hemgenix therapy.

There is limited data in patients with neutralising anti-AAV5 antibodies above 1:678. In 1 patient with a preexisting neutralising anti-AAV5 antibody titre of 1:3212 in the clinical study, no Factor IX expression was observed and restarting of exogenous Factor IX prophylaxis was needed (see section 5.1).

In the clinical studies with etranacogene dezaparvovec, for the patient sub-group with detectable preexisting neutralising anti-AAV5 antibodies up to a titre of 1:678, mean Factor IX activity levels were

within the same range but numerically lower compared to those of the patient sub-group without detectable preexisting neutralising anti-AAV5 antibodies. However, both patient groups, with and without detectable preexisting neutralising anti-AAV5 antibodies, demonstrated an improved haemostatic protection compared to the standard of care Factor IX prophylaxis after etranacogene dezaparvovec administration (see section 5.1).

Baseline hepatic function
Prior to the treatment with Hemgenix, patient`s liver transaminases should be evaluated and liver ultrasound and elastography performed. This includes:

- Enzyme testing (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin). ALT test results no later than within 3 months prior to treatment should be obtained, and ALT testing repeated at least once prior to Hemgenix administration to establish patient`s ALT baseline.
- Hepatic ultrasound and elastography assessment obtained no later than within 6 months before Hemgenix administration.

In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consideration of a consultation with a hepatologist is recommended to assess eligibility for Hemgenix administration (see information on hepatic function and Factor IX monitoring below).

Infusion-related reactions - During or shortly after Hemgenix infusion

Infusion reactions, including hypersensitivity reactions and anaphylaxis, are possible (see section 4.8). Patients should be closely monitored for infusion reactions throughout the infusion period and at least for 3 hours after end of infusion.
The recommended infusion rate provided in section 4.2 should be closely adhered to ensure patient tolerability.
Suspicion of an infusion reaction requires slowing or stopping of the infusion (see section 4.2). Based on clinical judgement, treatment with e.g. a corticosteroid or antihistamine may be considered for management of an infusion reaction.

Monitoring after the treatment with Hemgenix

Hepatotoxicity
Intravenous administration of a liver-directed AAV vector may potentially lead to liver transaminase elevations (transaminitis). The transaminitis is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the gene therapy.

In clinical studies with etranacogene dezaparvovec, transient, asymptomatic, and predominantly mild liver transaminase elevations were observed, most often in the first 3 months after etranacogene dezaparvovec administration. These transaminase elevations resolved either spontaneously or with corticosteroid treatment (see section 4.8).

To mitigate the risk of potential hepatotoxicity, patient`s liver transaminases should be evaluated and liver ultrasound and elastography performed before treatment (see section 4.2). After Hemgenix administration, transaminases should be closely monitored, e.g. once per week for at least 3 months. A course of corticosteroid taper should be considered in the event of ALT increase to above the upper limit of normal or to double the patient's baseline levels, along with human Factor IX activity examinations (see section 4.4 "Hepatic function and Factor IX monitoring"). Follow-up monitoring of transaminases in all patients who developed liver enzyme elevations is recommended on a regular basis until liver enzymes return to baseline values.

The safety of etranacogene dezaparvovec in patients with severe hepatic impairment, including cirrhosis, severe liver fibrosis (e.g. suggestive of or equal to METAVIR [Meta-analysis of Histological Data in Viral Hepatitis] Stage 3 disease or a liver elastography (FibroScan) score of ≥9 kPa), or uncontrolled Hepatitis B and C, have not been studied (see sections 4.3 and 5.2).

Factor IX assays
The results of Factor IX activity tests are lower if measured with chromogenic substrate assay (CSA) compared to one-stage clotting assay (OSA).
In clinical studies, the post-dose Factor IX activity measured with CSA returned lower values with the mean CSA to OSA Factor IX activity ratio ranging from 0.408 to 0.547 (see section 5.1).

Hepatic function and Factor IX monitoring
In the first 3 months after Hemgenix administration, the purpose of hepatic and Factor IX monitoring is to detect increases in ALT, which may be accompanied by decreased Factor IX activity and may indicate the need to initiate corticosteroid treatment (see sections 4.2 and 4.8). After the first 3 months of administration, hepatic and Factor IX monitoring is intended to routinely assess liver health and bleeding risk, respectively.

A baseline assessment of liver health (including liver function tests within 3 months and recent fibrosis assessment using either imaging modalities, such as ultrasound elastography, or laboratory assessments, within 6 months) should be obtained before administration of Hemgenix. Consider obtaining at least two ALT measurements prior to administration, or use an average of prior ALT measurements (for example within 4 months) to establish patient's baseline ALT. It is recommended that the hepatic function is evaluated through a multidisciplinary approach with involvement of a hepatologist to best adjust the monitoring to the patient's individual condition.

It is recommended (where possible) to use the same laboratory for hepatic testing at baseline and monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

After administration, the patient's ALT and Factor IX activity levels should be monitored according to Table 1. To assist in the interpretation of ALT results, monitoring of ALT should be accompanied by monitoring of AST and creatine phosphokinase (CPK) to help rule out alternative causes for ALT elevations (including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise). Based on patient's ALT elevations, corticosteroid treatment may be indicated (see Corticosteroid regimen). Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering.

Treating physicians should ensure the availability of patients for frequent monitoring of hepatic laboratory parameters and Factor IX activity after administration.

Table 1: Hepatic function and Factor IX activity monitoring

	Measurements	**Timeframe**	**Monitoring frequency[a]**
Before administration	Liver function tests Recent fibrosis assessment	Within 3 months prior to infusion Within 6 months prior to infusion	Baseline measurement
After administration	ALT[b] and Factor IX activity	First 3 months	Weekly

		Months 4 to 12 (Year 1)	Every 3 months
		Year 2	• Every 6 months for patients with Factor IX activity levels > 5 IU/dL (see Factor IX assays) • Consider more frequent monitoring in patients with Factor IX activity levels ≤ 5 IU/dL and consider the stability of Factor IX levels and evidence of bleeding.
		After Year 2	• Every 12 months for patients with Factor IX activity levels > 5 IU/dL (see Factor IX assays) • Consider more frequent monitoring in patients with Factor IX activity levels ≤ 5 IU/dL and consider the stability of Factor IX levels and evidence of bleeding.

[a] Weekly monitoring is recommended, or as clinically indicated, during corticosteroid tapering. Adjustment of the monitoring frequency may also be indicated depending on the individual situation.
[b] Monitoring of ALT should be accompanied by monitoring of AST and CPK, to rule out alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise).

If a patient returns to prophylactic use of Factor IX concentrates/haemostatic agents for haemostatic control, consider following monitoring and management consistent with instructions for those agents. An annual health check-up should include liver function tests.

Corticosteroid regimen
An immune response to the AAV5 capsid protein will occur after administration of etranacogene dezaparvovec. This may in some cases lead to elevation in liver transaminases (transaminitis) (see above and section 4.8). In case of elevated ALT levels above the upper limit of normal or doubling of the patient's baseline within the first 3 months post-dose, a corticosteroid treatment should be considered to dampen the immune response, e.g. starting with oral 60 mg/day prednisolone or prednisone (see Table 2). It is further recommended to assess possible alternative causes of the ALT elevation including administration of potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise. Retesting of ALT levels within 24 to 48 hours and, if clinically indicated, performing additional tests to exclude alternative aetiologies should be considered.

Table 2. Recommended prednisolone treatment in response to ALT elevations:

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 baseline level has been reached	Reduce daily dose by 5 mg/week

*Medicinal products equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other immunosuppressive therapy can also be considered in case of prednisolone treatment failure or contraindication (see section 4.5). It is further recommended to set a multidisciplinary consultation involving a hepatologist, to best adjust the alternative to corticosteroids and the monitoring to the patient's individual condition.

Risk of thromboembolic events

Patients with Haemophilia B have, compared to the general population, a reduced potential for thromboembolic events (e.g. pulmonary thromboembolism or deep venous thrombosis) due to inborn deficiency in the clotting cascade. Alleviating symptoms of Haemophilia B by restoring Factor IX activity may expose patients to the potential risk of thromboembolism, as observed in the general non-haemophilic population.

In patients with Haemophilia B with preexisting risk factors for thromboembolic events, such as a history of cardiovascular or cardiometabolic disease, arteriosclerosis, hypertension, diabetes, advanced age, the potential risk of thrombogenicity may be higher.

In the clinical studies with etranacogene dezaparvovec, treatment-related thromboembolic events were not reported (see section 5.1). In addition, no supraphysiological Factor IX activity levels were observed.

Contraceptive measures in relation to transgene DNA shedding in semen

Male patients should be informed on the need for contraceptive measures for them or their female partners of child bearing potential (see section 4.6).

Blood, organ, tissue and cell donation

Patients treated with Hemgenix must not donate blood, organs, tissues and cells for transplantation. This information is provided in the Patient Card which must be given to the patient after treatment.

Immunocompromised patients

No immunocompromised patients, including patients undergoing immunosuppressive treatment within 30 days before etranacogene dezaparvovec infusion, were enrolled in clinical studies with etranacogene dezaparvovec. Safety and efficacy of this medicinal product in these patients have not been established. Use in immunocompromised patients is based on healthcare professional`s judgment, taking into account the patient's general health and potential for corticosteroid use post-etranacogene dezaparvovec treatment.

HIV positive patients

Limited clinical data are available in patients with controlled HIV infection treated with etranacogene dezaparvovec (see sections 4.2 and 5.1).

The safety and efficacy in patients with HIV infection not controlled with anti-viral therapy, as shown by CD4+ counts ≤200/µL, was not established in clinical studies with etranacogene dezaparvovec (see section 4.3).

Patients with active or uncontrolled chronic infections

There is no clinical experience with administration of etranacogene dezaparvovec in patients with acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as active chronic Hepatitis B). It is possible that such acute or uncontrolled infections may affect the response to Hemgenix and reduce its efficacy and/or cause adverse reactions. In patients with such infections, Hemgenix treatment is contraindicated (see section 4.3).

If there are signs or symptoms of acute or uncontrolled chronic active infections, Hemgenix treatment must be postponed until the infection has resolved or is controlled.

Patients with Factor IX inhibitors, Monitoring for Factor IX inhibitor development

There is no clinical experience with administration of etranacogene dezaparvovec in patients who have or had inhibitors to Factor IX. It is not known whether or to what extent such preexisting Factor IX inhibitors may affect the safety or efficacy of Hemgenix. In patients with a history of Factor IX inhibitors, Hemgenix treatment is not indicated (see section 4.1).

In the clinical studies with etranacogene dezaparvovec, patients had no detectable Factor IX inhibitors at baseline, and formation of inhibitors to etranacogene dezaparvovec was not observed after treatment (see section 5.1).

Patients should be monitored through appropriate clinical observations and laboratory tests for the development of inhibitors to Factor IX after Hemgenix administration.

Use of Factor IX concentrates or haemostatic agents after treatment with etranacogene dezaparvovec

Following administration of etranacogene dezaparvovec:

- Factor IX concentrates/haemostatic agents may be used in case of invasive procedures, surgery, trauma, or bleeds, consistent with current treatment guidelines for the management of Haemophilia, and based on the patient's current Factor IX activity levels.
- If the patient's Factor IX activity levels are consistently below 5 IU/dL and the patient has experienced recurrent spontaneous bleeding episodes, physicians should consider the use of Factor IX concentrates to minimise such episodes, consistent with current treatment guidelines for the management of Haemophilia. Target joints should be treated in accordance with relevant treatment guidelines.

Repeated treatment and impact to other AAV-mediated therapies

It is not yet known whether or under what conditions Hemgenix therapy may be repeated, and to what extent developed endogenous cross-reacting antibodies could interact with the capsids of AAV vectors used by other gene therapies, potentially impacting their treatment efficacy (see section 4.4 further above).

Risk of malignancy as a result of vector integration

Integration site analysis was performed on liver samples from one patient treated with Hemgenix in clinical studies. Samples were collected one year post-dose. Vector integration into human genomic DNA was observed in all samples.
The clinical relevance of individual integration events is not known to date, but it is acknowledged that individual integration into human genome could potentially contribute to a risk of malignancy.

In the clinical studies, no malignancies were identified in relation to treatment with etranacogene dezaparvovec (see sections 5.1 and 5.3). In the event that a malignancy occurs, the marketing authorisation holder should be contacted by the treating healthcare professional to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis.

It is recommended that patients with preexisting risk factors for hepatocellular carcinoma (such as hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations (e.g. annually) for at least 5 years after Hemgenix administration (see also section 4.3).

Long-term follow up

Patients are expected to be enrolled in a follow-up study to follow Haemophilia patients for 15 years, to substantiate the long-term safety and efficacy of Hemgenix gene therapy.

Sodium and potassium content

This medicinal product contains 35.2 mg sodium per vial, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, that is to say essentially potassium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Prior to etranacogene dezaparvovec administration, the patient's existing medicinal products should be reviewed to determine if they should be modified to prevent anticipated interactions described in this section.

Patients' concomitant medications should be monitored after etranacogene dezaparvovec administration, particularly during the first year, and the need to change concomitant medicinal products based on patient's hepatic health status and risk should be evaluated. When a new medication is started, close monitoring of ALT and Factor IX activity levels (e.g. weekly to every 2 weeks for the first month) is recommended to assess potential effects on both levels.

No *in vivo* interaction studies have been performed.

Hepatotoxic medicinal products or substances

Experience with use of this medicinal product in patients receiving hepatotoxic medications or using hepatotoxic substances is limited. Safety and efficacy of etranacogene dezaparvovec in these circumstances have not been established (see section 4.4).

Before administering etranacogene dezaparvovec to patients receiving potentially hepatotoxic medicinal products or using other hepatotoxic agents (including alcohol, potentially hepatotoxic herbal products and nutritional supplements) and when deciding on the acceptability of such agents after treatment with etranacogene dezaparvovec, physicians should consider that they may reduce the efficacy of etranacogene dezaparvovec and increase the risk for more serious hepatic reactions, particularly during the first year following etranacogene dezaparvovec administration (see section 4.4).

Interactions with agents that may reduce or increase plasma concentrations of corticosteroids

Agents that may reduce or increase the plasma concentration of corticosteroids (e.g. agents that induce or inhibit cytochrome P450 3A4) can decrease the efficacy of the corticosteroid regimen or increase their side effects (see section 4.4).

Vaccinations

Prior to etranacogene dezaparvovec infusion, ensure that the patient's vaccinations are up to date. The patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy (see section 4.4). Live vaccines should not be administered to patients while on immunomodulatory therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

No dedicated animal fertility/embryofoetal studies have been conducted to substantiate whether the use in women of childbearing potential and during pregnancy could be harmful for the newborn child (theoretical risk of viral vector integration in foetal cells through vertical transmission).
No data are available to recommend a specific duration of contraceptive measures in women of childbearing potential. Therefore, Hemgenix is not recommended in women of childbearing potential.

Contraception after administration in males

In clinical studies, after administration of etranacogene dezaparvovec, transgene DNA was temporarily detectable in semen (see section 5.2).

For 12 months after administration of etranacogene dezaparvovec treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception.
Males treated with Hemgenix must not donate semen to minimise the potential risk of paternal germline transmission (see section 4.4).

Pregnancy

Experience regarding the use of this medicinal product during pregnancy is not available. Animal reproduction studies have not been conducted with Hemgenix. It is not known whether this medicinal product can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Hemgenix should not be used during pregnancy.

Breast-feeding

It is unknown whether etranacogene dezaparvovec is excreted in human milk. A risk to the newborns/infants cannot be excluded. Hemgenix should not be used during breast feeding.

Fertility

Effects on male fertility have been evaluated in animal studies with mice. No adverse impact on the fertility was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Infusion of etranacogene dezaparvovec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as temporary dizziness, fatigue, and headache that have occurred shortly after etranacogene dezaparvovec administration, patients should be advised to use caution when driving and operating machinery until they are certain that this medicinal product does not adversely affect them (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) in clinical studies with etranacogene dezaparvovec were headache (very common; 31.6% of patients), ALT elevations (very common; 22.8% of patients), AST elevations (very common; 17.5% of patients), and influenza-like illness (very common; 14% of patients).

Tabulated list of adverse reactions

The Table 3 shows the overview of ADRs from clinical trials with etranacogene dezaparvovec in 57 patients. The ADRs are classified according the MedDRA System Organ Class and frequency. The ADRs are listed based on the following convention for frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000),

and not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing frequency.

Table 3. Adverse drug reactions obtained from clinical studies with etranacogene dezaparvovec

MedDRA System Organ Class (SOC)	ADR (Preferred term)	Frequency per patient
Nervous system disorders	Headache	Very common
	Dizziness	Common
Gastrointestinal disorders	Nausea	Common
General disorders and administration site conditions Investigations	Influenza like illness	Very common
	Fatigue, malaise	Common
	Alanine aminotransferase increased, aspartate aminotransferase increased, C-reactive protein increased	Very common
	Blood creatine phosphokinase increased, blood bilirubin increased	Common
Injury, poisoning and procedural complications	Infusion related reaction (Hypersensitivity, infusion site reaction, dizziness, eye pruritus, flushing, abdominal pain upper, urticaria, chest discomfort, pyrexia)	Very Common*

*The frequency results from pooled infusion related reactions of similar medical concept. Individual infusion reactions occurred in 1 to 2 subjects with common frequency (incidence of 1.8 to 3.5%).

Hepatic laboratory Abnormalities

Table 4 describes hepatic laboratory abnormalities following administration of Hemgenix. ALT increases are further characterised, as they may be accompanied by decreased Factor IX activity and may indicate the need to initiate corticosteroid treatment (see section 4.4).

Table 4. Hepatic laboratory abnormalities in patients administered 2 x 10^{13} gc/kg body weight etranacogene dezaparvovec in clinical studies

Laboratory Parameter Increases[a]	Number of patients (%) N = 57
ALT increases > ULN[b]	**23 (40.4%)**
> ULN – 3.0 x ULN[c]	17 (29.8%)
> 3.0 – 5.0 x ULN[d]	1 (1.8%)
> 5.0 – 20.0 x ULN[e]	1 (1.8%)
AST increases > ULN[b]	**24 (42.1%)**
> ULN – 3.0 x ULN[c]	19 (33.3%)
> 3.0 – 5.0 x ULN[d]	4 (7.0%)
Bilirubin increases > ULN[b]	**14 (24.6%)**
> ULN – 1.5 x ULN[c]	12 (21.1%)

Abbreviations: ULN = Upper Limit of Normal; CTCAE = Common Terminology Criteria for Adverse Events

[a]Highest post-dose CTCAE Grades of values are presented

[b]Not all patients with laboratory abnormality >ULN reached CTCAE Grade 1 due to elevated baseline levels

[c]CTCAE Grade 1

[d]CTCAE Grade 2

[e]CTCAE Grade 3

Description of selected adverse reactions

Infusion related reactions

In the clinical studies with etranacogene dezaparvovec, infusion-related reactions of mild to moderate severity have been observed in 7/57 (12.3%) subjects. The infusion was temporarily interrupted in 3 patients and resumed at a slower infusion rate upon treatment with antihistamines and/or corticosteroids. In 1 patient, infusion was stopped and not resumed (see section 5.1).

Immune-mediated transaminitis
In the clinical studies, treatment-emergent adverse reactions of ALT increases occurred in 13/57 (22.8%) patients. The onset of ALT elevations ranged from day 22 to 787 post-dose. Nine of the 13 patients with ALT elevations received a tapered course of corticosteroid. The mean corticosteroid treatment duration for those patients was 81.4 days. Nine of the 13 patients with ALT elevations also experienced AST elevations. All treatment-emergent adverse events of elevated ALTs were non-serious and resolved within 3 to 127 days.

Immunogenicity
In the clinical studies with etranacogene dezaparvovec, no Factor IX inhibitor development was observed.

An expected sustained humoral immune response to the infused AAV5 capsid was observed in all patients treated with etranacogene dezaparvovec. Anti-AAV5 antibody levels raised above the upper limit of quantification of 1:8748 by week 3 post-dose and remained elevated above the upper limit of quantification, as measured at month 24 post-dose.

Reporting of suspected adverse reactions

Reporting suspected adverse drug reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no clinical study data regarding overdose with etranacogene dezaparvovec.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood coagulation factors, ATC code: B02BD16

Mechanism of action

Etranacogene dezaparvovec is a gene therapy product designed to introduce a copy of the human Factor IX coding DNA sequence into hepatocytes to address the root cause of the Haemophilia B disease. Etranacogene dezaparvovec consists of a codon-optimised coding DNA sequence of the gain-of-function Padua variant of the human Factor IX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5) (see section 2.1).
Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form (see section 5.3 below). After transduction, etranacogene dezaparvovec directs long-term liver-specific expression of Factor IX-Padua protein. As a result, etranacogene dezaparvovec partially or completely ameliorates the deficiency of circulating Factor IX procoagulant activity in patients with Haemophilia B.

Clinical efficacy and safety

The safety and efficacy of etranacogene dezaparvovec was evaluated in 2 prospective, open-label, single-dose, single-arm studies, a phase 2b study performed in US and a phase 3 multi-national study performed in US, UK and EU. Both studies enrolled adult male patients (body weight range: 58 to 169 kg) with moderately severe or severe Haemophilia B (≤2% of Factor IX activity; N=3 in phase 2b and N=54 in phase 3), who received a single intravenous dose of 2×10^{13} gc/kg body weight of etranacogene dezaparvovec and entered a follow-up period of 5 years.

In the pivotal phase 3 study, a total of N=54 male patients, aged 19 to 75 at enrollment (n=47 ≥18 and < 65 years; n=7 ≥ 65 years) with moderately severe or severe Haemophilia B completed a ≥6-month observational lead-in phase with standard of care routine Factor IX prophylaxis after which the patients received a single intravenous dose of etranacogene dezaparvovec. Post-treatment follow-up visits occurred regularly, with 53/54 patients completing at least 18 months of follow-up. One patient, aged 75 at screening, died of cardiogenic shock at month 15 post-dose, an event confirmed not treatment-related. The remaining 53/54 patients continue follow-up for a total of 5 years post-dose. Of these, 1 patient received a partial dose (10%) of etranacogene dezaparvovec due to an infusion reaction during infusion. All patients were on prophylactic Factor IX replacement therapy prior to dosing with etranacogene dezaparvovec. Preexisting neutralising anti-AAV5 antibodies were present in 21/54 (38.9%) patients at baseline.
The primary efficacy objective for the phase 3 study was to assess the annualised bleeding rate (ABR) reduction between month 7 and 18 post-dose, i.e., after establishment of stable Factor IX expression by month 6 post-dose, compared to the observational lead-in period. For this purpose, all bleeding episodes, regardless of investigator assessment, were considered. The efficacy results showed superiority of etranacogene dezaparvovec to continuous routine Factor IX prophylaxis (see Table 5).

Table 5. Bleeding events and Annualised Bleeding Rates

Number	**≥6-month lead-in period FAS (N=54)**	**7-18 months post-dose FAS (N=54)**	**≥6-month lead-in period (N=53)*** **	**7-18 months post-dose (N=53)*** **
Number of patients with bleeds	40 (74.1%)	20 (37.0%)	40 (75.5%)	19 (35.8%)
Number of patients with zero bleeds	14 (25.9%)	34 (63.0%)	13 (24.5%)	34 (64.2%)
Number of any bleeds	136	54	136	49
Number of person years for bleeding events	33.12	49.78		
Adjusted* ABR** (95% CI) for any bleeds	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)	3.89 (2.93, 5.16)	1.07 (0.63, 1.82)
ABR reduction (lead-in to post-treatment) 2-sided 95% Wald CI 1-sided p-value****	-	64% (36%, 80%) 0.0002		72% (57%, 83%) p<0.0001
Number of patients with severe bleeds	10 (18.5%)	7 (13%)	-	-
Number of patients with very severe bleeds	3 (5.6%)	2 (3.7%)	-	-
Adjusted ABR for spontaneous bleeds 1-sided p-value	1.52	0.44 p=0.0034	-	-
Adjusted ABR for joint bleeds 1-sided p-value	2.35	0.51 p<0.0001	-	-
Adjusted ABR for traumatic bleeds 1-sided p-value	2.09	0.62 p<0.0001	-	-

Abbreviations: ABR = annualised bleeding rate; FAS = Full Analysis Set including all 54 patients dosed; CI = confidence interval

*Adjusted ABR: Adjusted ABR rate and comparison of ABR between lead-in and post-treatment period was estimated from a statistical modelling (i.e., from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.)

**The ABR was measured from month 7 to month 18 after etranacogene dezaparvovec infusion, ensuring this period represented steady-state Factor IX expression from the transgene.

***The population data includes all patients dosed except for one patient with the preexisting neutralising anti-AAV5 antibody titre of 1:3212 who did not respond to treatment, i.e., did not show Factor IX expression and activity post-dose.

****1-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant.

After single-dose of etranacogene dezaparvovec, clinically relevant increases in Factor IX activity were observed, as measured by the one-stage (aPTT-based) assay (see Table 6). Factor IX activity was also measured with chromogenic assay and the results were lower compared to the results of the one-stage (aPTT-based) assay with the mean chromogenic to one-stage Factor IX activity ratio ranging from 0.408 to 0.547 from month 6 to month 24 post-dose.

Table 6. Uncontaminated[2] Factor IX activity at 6, 12, 18 and 24 months (FAS; one-stage (aPTT-based) assay)

	Baseline[1] (N=54)[2]	**6 months post-dose (N=51)[2]**	**12 months post-dose (N=50)[2]**	**18 months post-dose (N=50)[2]**	**24 months post-dose[5] (N=50)[2]**
Mean % (SD)	1.19 (0.39)	38.95 (18.72)	41.48 (21.71)	36.90 (21.40)	36.66 (18.96)
Median % (min, max)	1.0 (1.0, 2.0)	37.30 (8.2, 97.1)	39.90 (5.9, 113.0)	33.55 (4.5, 122.9)	33.85 (4.7, 99.2)
Change from baseline Least Squares (LS) mean (SE)[3] 95% CI 1-sided p-value[4]	n.a.	36.18 (2.432) 31.41, 40.95 p<0.0001	38.81 (2.442) 34.01, 43.60 p<0.0001	34.31 (2.444) 29.52, 39.11 p<0.0001	34.13 (2.325) 29.57, 38.69 p<0.0001

Abbreviations: aPTT = activated Partial Thromboplastin Time; CI = confidence interval; FAS = Full Analysis Set including all 54 patients dosed; LS = least squares; max = maximum; min = minimum; n.a. = not applicable; SD = standard deviation; SE = standard error.

[1]Baseline: baseline Factor IX activity was imputed based on subject's historical Haemophilia B severity documented on the case report form. If the subject had documented severe Factor IX deficiency (Factor IX plasma level <1%), their baseline Factor IX activity level was imputed as 1%. If the subject had documented moderately severe Factor IX deficiency (Factor IX plasma level ≥1% and ≤2%) their baseline Factor IX activity level was imputed as 2%.

[2]Uncontaminated: the blood samples collected within 5 half-lives of exogenous Factor IX use were excluded. Both the date and time of exogenous Factor IX use and blood sampling were considered in determining contamination. Patients with zero uncontaminated central laboratory post-treatment values had their change from baseline assigned to zero for this analysis, and had their post-baseline values set equal to their baseline value. Baseline Factor IX was imputed based on patients' historical Haemophilia B severity documented on the case report form. The FAS included 1 patient who received only 10% of the planned dose, 1 patient who died at month 15 post-dose due to unrelated concomitant disease, 1 patient with 1:3212 titre of preexisting neutralising anti-AAV5 antibodies who did not respond to treatment, and 1 patient with contamination with exogenous Factor IX. Accordingly, the population data included 54 to 50 patients with uncontaminated sampling.

[3]Least Squares Mean (SE): mean from repeated measures linear mixed model with visit as a categorical covariate.

[4]1-sided p-value ≤0.025 for post-treatment above baseline was regarded as statistically significant.

[5]For month 24, data was based on an ad-hoc analysis and the p-value was not adjusted for multiplicity.

The onset of Factor IX protein expression post-dose was detectable from the first uncontaminated measurement at week 3. In general, although more variable, Factor IX protein kinetic profile during the post-treatment period followed a trend similar to Factor IX activity.
Durability analysis of Factor IX activity showed stable Factor IX levels from 6 months up to 24 months. The durability analysis showed a similar trend of post-dose Factor IX activity for etranacogene dezaparvovec as for the predecessor, the rAAV5-hFIX gene therapy encoding wild type human Factor IX in a preceding clinical study, which showed stable post-dose Factor IX activity from 6 months up to 5 years (see section 5.3).

While overall numerically lower mean Factor IX activity was observed in patients with preexisting neutralising anti-AAV5 antibodies, no clinically meaningful correlation was identified between patients` preexisting anti-AAV5 antibody titre and their Factor IX activity at 18 months post-dose (see Table 7). In 1 patient with a titre of 1:3212 for preexisting anti-AAV5 antibodies at screening, no response to etranacogene dezaparvovec treatment was observed, with no Factor IX expression and activity.

Table 7. Endogenous Factor IX activity levels post-dose in patients with and without preexisting neutralising anti-AAV5 antibodies (FAS; one-stage (aPTT-based) assay)

				Change from Baseline		
	Number of patient	**Mean Factor IX activity (%) (SD)**	**Median Factor IX activity (%) (min, max)**	**Least Squares mean (SE)[†]**	**95% CI**	**1-sided p-value**
With preexisting neutralising anti-AAV5 antibodies						
Baseline	21	1.24 (0.44)	1.00 (1.0, 2.0)	n.a.	n.a.	n.a.
Month 6	18	35.91 (19.02)	36.60 (8.2, 90.4)	30.79 (3.827)	23.26, 38.32	<0.0001
Month 12	18	35.54 (17.84)	39.95 8.5, 73.6)	31.59 (3.847)	24.02, 39.16	<0.0001
Month 18	17	31.14 (13.75)	32.00 (10.3, 57.9)	26.83 (3.854)	19.24, 34.41	<0.0001
Month 24	17	32.98 (18.51)	33.50 (9.1, 88.3)	28.35 (3.928)	20.62, 36.08	<0.0001
Without preexisting neutralising anti-AAV5 antibodies						
Baseline	33	1.15 (0.36)	1.00 (1.0, 2.0)	n.a.	n.a.	n.a.
Month 6	33	40.61 (18.64)	37.30 (8.4, 97.1)	39.46 (3.172)	33.23, 45.69	<0.0001
Month 12	32	44.82 (23.21)	38.65 (5.9, 113.0)	43.07 (3.176)	36.83, 49.31	<0.0001
Month 18	33	39.87 (24.08)	35.00 (4.5, 122.9)	38.72 (3.172)	32.49, 44.95	<0.0001
Month 24	33	38.55 (19.19)	35.40 (4.7, 99.2)	37.40 (2.933)	31.64, 43.16	<0.0001

Abbreviations: FAS = Full Analysis Set including all 54 patients dosed; aPTT = activated partial thromboplastin time; CI = confidence interval; LS = least square; max = maximum; min = minimum; n.a. = not applicable; SD = standard deviation; SE = standard error.
[†]Least squares mean (SE): from repeated measures linear mixed model with visit as a categorical covariate.

The study also demonstrated superiority of etranacogene dezaparvovec at 18-months post-dose over the routine exogenous Factor IX prophylaxis in the lead-in period (see Table 8). The ABR for Factor IX-treated bleeding episodes during the month 7 to 18 post-dose period was reduced by 77% (see Table 5).

Table 8. Annualised Bleeding Rates for Factor IX-treated bleeding episodes

	≥6-month lead-in period FAS (N=54)	**7-18 months post-dose FAS (N=54)**
Number of patients with Factor IX-treated bleeds	37/54 (68.5%)	15/54 (27.8%)
Number of Factor IX-treated bleeds	118	30
Adjusted ABR (95% CI) for Factor IX-treated bleeds	3.65 (2.82, 4.74)	0.84 (0.41, 1.73)
ABR ratio for Factor IX-treated bleeds (post-treatment to lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.23 (0.12, 0.46) p<0.0001
Adjusted ABR (95% CI) for spontaneous bleeds treated with Factor IX	1.34 (0.87, 2.06)	0.45 (0.15, 1.39)
ABR ratio for spontaneous bleeds treated with Factor IX (post-treatment to lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.34 (0.11, 1.00) p= 0.0254
Adjusted ABR (95% CI) for joint bleeds treated with Factor IX	2.13 (1.58, 2.88)	0.44 (0.19, 1.00)
ABR ratio for joint bleeds treated with Factor IX (post-treatment to lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.20 (0.09, 0.45) p<0.0001

Abbreviations: ABR = annualised bleeding rate; FAS = Full Analysis Set including all 54 subjects dosed; CI = confidence interval

The mean consumption of Factor IX replacement therapy significantly decreased by 248,825.0 IU/year/patient (98.42%; 1-sided p< 0.0001) between month 7 and 18 and by 248.392.6 IU/year/patient (96.52%; 1-sided p< 0.0001) between month 7 to 24 following treatment with etranacogene dezaparvovec compared to standard of care routine Factor IX prophylaxis during the lead-in period. From day 21 through to months 7 to 24, 52 of 54 (96.3%) treated patients remained free of continuous routine Factor IX prophylaxis.

Overall, similar results were observed at 24 months post-dose in the phase 3 study. Of note, none of the patients showed evidence of neutralising inhibitors to etranacogene dezaparvovec-derived Factor IX over 2 years post-dose. Similarly, none of the 3 patients enrolled in the phase 2b study showed evidence of neutralising inhibitors over the period of 3 years post-dose. The 3 patients demonstrated clinically relevant increases in Factor IX activity and discontinued their routine Factor IX replacement prophylaxis over the period of 3 years post-dose.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Hemgenix in one or more subsets of the paediatric population in the treatment of Haemophilia B (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Distribution, biotransformation and elimination

The etranacogene dezaparvovec-derived Factor IX protein produced in the liver is expected to undergo similar distribution and catabolic pathways as the endogenous native Factor IX protein in people without Factor IX deficiency (see section 5.1).

Clinical pharmacokinetics of shedding

The pharmacokinetics of shedding was characterised following etranacogene dezaparvovec administration, using a sensitive polymerase chain reaction (PCR) assay to detect vector DNA sequences in blood and semen samples, respectively. This assay is sensitive to transgene DNA, including fragments of degraded DNA. It does not indicate whether DNA is present in the vector capsid, in cells or in the fluid phase of the matrix (e.g. blood plasma, seminal fluid), or whether intact vector is present.

In the phase 3 study, detectable vector DNA with a maximum vector DNA concentrations post-dose was observed in blood (n = 53/54) and semen (n = 42/54) at a median time (T_{max}) of 4 hours and 42 days, respectively. The mean peak concentrations were 2.2×10^{10} copies/mL and 3.8×10^{5} copies/mL in blood and semen, respectively. After reaching the maximum in a matrix, the transgene DNA concentration declines steadily. Shedding-negative status in patients was defined as having 3 consecutive samples at vector DNA concentration below the limit of detection (<LOD). Using this definition, a total of 56% (30/54) of patients reached absence of vector DNA from blood and 69% (37/54) from semen by month 24. The median time to absence of shedding was 52.3 weeks in blood and 45.8 weeks in semen at 24 months post-dose. Several subjects did not return the required number of blood and semen samples to assess the shedding status as per the definition. Considering shedding results obtained from the final 2 available consecutive samples, a total of 40/54 (74%) and 47/54 (87%) patients were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post-dose.

Pharmacokinetics in special populations

Patients with renal impairment
In the phase 3 study, majority (n=45) of the patients had normal renal function (creatinine clearance (CLcr) = ≥90 mL/min defined by Cockcroft-Gault equation), 7 patients had mild renal impairment (CLcr = 60 to 89 mL/min) and 1 patient had moderate renal impairment (CLcr = 30 to 59 mL/min). No clinically relevant differences in Factor IX activity were observed between these patients.

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

Patients with hepatic impairment
In the phase 3 study, patients with varying degree of liver steatosis at baseline showed no clinically relevant different Factor IX activity levels.

Patients with severe liver impairment and advanced fibrosis were not studied (see section 4.2 and 4.4).

5.3 Preclinical safety data

General toxicity

Preclinical studies were initiated with a gene therapy product employing the recombinant adeno-associated virus serotype 5 (rAAV5) expressing the wild type of the human coagulation Factor IX (rAAV5-hFIX). Etranacogene dezaparvovec (rAAV5-hFIX-Padua) was subsequently developed from rAAV5-hFIX by introduction of a 2 nucleotide change in the transgene for human Factor IX, generating thereby the naturally occurring Padua variant of Factor IX, which exhibits significantly augmented activity (see section 5.1).

The No Observed-Adverse-Effect-Level (NOAEL) was observed at $9x10^{13}$ gc/kg body weight in non-human primates, which is approximately 5-fold above the human etranacogene dezaparvovec dose of $2x10^{13}$ gc/kg body weight.
Biodistribution of etranacogene dezaparvovec and its predecessor, the gene therapy of human wild type Factor IX, was assessed in mice and non-human primates following intravenous administration (see section 5.3). Dose-dependent preferential distribution to the liver was confirmed for both vectors and their transgene expression.

Genotoxicity

Genotoxic and reproductive risks were evaluated with the rAAV5-hFIX. The integration site analysis in host genomic DNA was performed on liver tissue from mice and non-human primates injected with rAAV5-hFIX up to a dose of 2.3×10^{14} gc/kg body weight, corresponding to approximately 10-fold higher than the clinical dose in human. The retrieved rAAV5-hFIX vector DNA sequences represented almost exclusively episomal forms that were non-integrated into the host DNA. The remaining low level of integrated rAAV5-hFIX DNA was distributed throughout the host genome with no preferred integration in genes associated with mediation of malignant transformation in human (see section 4.4 Risk of malignancy as a result of vector integration).

Carcinogenicity

No dedicated carcinogenicity studies were performed with etranacogene dezaparvovec.
Although there are no fully adequate animal models to address the tumorigenic and carcinogenic potential of etranacogene dezaparvovec in human, toxicological data do not suggest concern for tumourigenicity.

Reproductive and developmental toxicity

No dedicated reproductive and developmental toxicity studies, including embryo foetal and fertility assessments, were performed with etranacogene dezaparvovec, as males comprise the majority of the patient population to be treated with Hemgenix. The risk of germline transmission after administration of $2.3x10^{14}$ gc/kg body weight rAAV5-hFIX, i.e. a dose approximately 10-fold higher than recommended for humans, was assessed in mice. The rAAV5-hFIX administration resulted in detectable vector DNA in the reproductive organs and sperm of male animals. However, following mating of these mice with naïve female animals at 6 days after administration, the rAAV5-hFIX vector DNA was not detected in the female reproductive tissues nor offspring, indicating no paternal germline transmission.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate-20
Potassium chloride
Potassium phosphate
Sodium chloride
Sodium phosphate
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

After dilution

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection (see section 6.6), Hemgenix can be stored at 15 °C - 25 °C in the infusion bag protected from light. However, the administration of etranacogene dezaparvovec dose to the patient should be completed within 24 hours after the dose preparation.
The stability after dilution was established for Polyethylene/Polypropylene (PE/PP) copolymer, Polyvinyl chloride (PVC)-free infusion bags with sodium chloride 9 mg/mL (0.9%) solution for injection.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
Dilute before use.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL solution in a Type I glass vial with stopper (chlorobutyl rubber), aluminium seal with a flip-off cap.

Hemgenix is supplied in a vial containing 10 mL.

The total number of vials in each finished pack corresponds to the dosing requirement of the individual patient, depending on the body weight, and is provided on the package.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms (GMOs).

Personal protective equipment, including gloves, safety goggles, protective clothing and masks, should be worn while preparing and administering etranacogene dezaparvovec.

Preparation of etranacogene dezaparvovec prior to administration

1. Use aseptic techniques during the preparation and administration of etranacogene dezaparvovec.
2. Use etranacogene dezaparvovec vial(s) only once (single-use vial(s)).
3. Verify the required dose of etranacogene dezaparvovec based on the patient's body weight. The total number of vials in each finished pack corresponds to the dosing requirement for each individual patient based on the body weight.
4. Etranacogene dezaparvovec must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration.
    - Withdraw the volume of the calculated Hemgenix dose (in mL) from the 500 mL-infusion bag(s) with sodium chloride 9 mg/mL (0.9%) solution for injection. The volume to be withdrawn will vary based on the patient body weight.
        - For patients <120 kg body weight, withdraw the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from one 500 mL-infusion bag.
        - For patients ≥120 kg body weight, withdraw the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from two

500 mL-infusion bags, by withdrawing half of the volume from each of the two 500 mL-infusion bags.
- Add subsequently the required etranacogene dezaparvovec dose to the infusion bag(s) to bring the total volume in each infusion bag back to 500 mL.

5. Add the Hemgenix dose directly into the sodium chloride 9 mg/mL (0.9%) solution for injection. Do not add the Hemgenix dose into the air in the infusion bag during diluting.
6. Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
7. To avoid foaming:
   - Do not shake the etranacogene dezaparvovec vial(s) and the prepared infusion bag(s).
   - Do not use filter needles during preparation of etranacogene dezaparvovec.
8. To reduce the risk of spillage and/or aerosol formation, the infusion bag(s) should be provided connected to an infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
9. The infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be connected to the main intravenous infusion line also primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection prior to use.
10. Use only sodium chloride 9 mg/mL (0.9%) solution for injection since the stability of etranacogene dezaparvovec has not been determined with other solutions and diluents.
11. Do not infuse the diluted etranacogene dezaparvovec solution in the same intravenous line with any other products.
12. Do not use a central line or port.

Administration

13. Diluted etranacogene dezaparvovec should be visually inspected prior to administration. The diluted etranacogene dezaparvovec should be a clear, colourless solution. If particulates, cloudiness or discoloration are visible in the infusion bag, do not use etranacogene dezaparvovec.
14. Use the product after dilution as soon as possible. You must not exceed the storage time of the diluted product beyond that provided section 6.3.
15. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES).
16. The diluted etranacogene dezaparvovec solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
17. Etranacogene dezaparvovec solution should be infused closely following the infusion rate(s) provided in section 4.2. The administration should be completed within ≤24 hours after the dose preparation (see section 4.2).
18. After the entire content of the infusion bag(s) is infused, the infusion line must be flushed at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure all etranacogene dezaparvovec is delivered.

Measures to take in case of accidental exposure

In case of accidental exposure local guidance for pharmaceutical waste must be followed.

- In case of accidental exposure to eyes, immediately flush eyes with water for at least 15 minutes. Do not use alcohol solution.
- In case of accidental needle stick exposure, encourage bleeding of the wound and wash injection area well with soap and water.
- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. Do not use alcohol solution.
- In case of accidental inhalation, move the person into fresh air.
- In case of accidental oral exposure, abundantly rinse mouth with water.
- In each case, obtain subsequently medical attention.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable materials that may have come in contact with Hemgenix (solid and liquid waste) must be disposed of in compliance with the local guidance for pharmaceutical waste. Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during Hemgenix use.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage and then autoclaved, if possible.

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
D-35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1715/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 2023
Date of first renewal: 07 December 2023

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

uniQure, Inc.
113 Hartwell Avenue
Lexington, MA 02421
US

Name and address of the manufacturer(s) responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Hemgenix in each Member State, the marketing authorisation holder (MAH) must agree about the content and format of the educational program with the National Competent Authorities.

The MAH shall ensure that in each Member State where Hemgenix is marketed, all healthcare professionals and patients/carers who are expected to prescribe, use or oversee the administration of Hemgenix have access to/are provided with the following educational packages. These packages will be translated in the local language to ensure understanding of proposed mitigation measures by physicians and patients:

- Physician Educational Material
- Patient Information Pack.

The Physician Educational Material consists of:

- Guide for Healthcare Professionals;
- The Summary of Product Characteristics;
- The Patient/Care-giver guide;
- The Patient Card.

The Patient Information Pack consists of:

- The Patient/Care-giver guide;
- The Patient Card;
- The patient information leaflet.

The Guide for Healthcare Professionals key messages:

- To inform the patient of the important identified risk of hepatotoxicity and the important potential risks of horizontal and germline transmission, development of Factor IX inhibitors, malignancy in relation to vector genome integration, and thromboembolism, and details on how these risks can be minimised.
- Before a treatment decision is made, the healthcare professional should discuss the risks, benefits, and uncertainties of Hemgenix with the patient when presenting Hemgenix as a treatment option, including:
    - That Hemgenix use will require in some cases administration of corticosteroids to manage the liver damage that this medicinal product might induce. This requires adequate monitoring of patients' liver function and avoidance of concomitant use of hepatotoxic medication or agents, to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of Hemgenix.
    - That high preexisting neutralising anti-AAV5 antibodies may reduce the efficacy of Hemgenix therapy; patients should be assessed for the titre of preexisting neutralising anti-AAV5 antibodies before Hemgenix treatment.
    - That there is a possibility of not responding to treatment with Hemgenix. Patients who do not respond are still exposed to long-term risks.
    - That the long-term treatment effect cannot be predicted.
    - That there would be no plans to re-administer the medicinal product for patients who do not respond or have lost the response.
    - That the patients should be tested for Factor IX inhibitors to monitor development of Factor IX inhibitors.
    - Reminding patients about the importance to enroll in a registry for follow up of long-term effects.
    - The healthcare professional should provide the patient guide and patient card to the patient.

The Patient/Care-giver Guide key messages:

- Importance to fully understand the benefits and risks of Hemgenix treatment, what is known and not yet known about the long-term effects, related to both safety and efficacy.
- Therefore, before a decision is made about starting on the therapy the doctor will discuss with the patient the following:
    - That Hemgenix will, in some cases, require treatment with corticosteroids to overcome the liver damage that this medicine may produce, and that the doctor will ensure that patients are available for regular blood tests to check response to Hemgenix and assess liver health.

Patients should inform the healthcare professional about current use of corticosteroids or other immunosuppressants. If the patient cannot take corticosteroids, the doctor may recommend alternative medicines to manage problems with the liver.

- That high preexisting immunity against the vector may reduce the efficacy of Hemgenix therapy; patients are expected to be assessed for the titre of preexisting neutralising anti-AAV5 antibodies before the Hemgenix treatment.
- That not all patients may benefit from treatment with Hemgenix. Patients not responding to treatment are still be exposed to long-term risks.
- Details how the important potential risks of horizontal and germline transmission, development of Factor IX inhibitors, malignancy in relation to vector genome integration, and thromboembolism can be recognised and minimised by regular monitoring as recommended by doctors, including that:
  - The patient should seek immediate medical advice for any symptoms suggestive of a thromboembolic event.
  - Male patients of reproductive potential or their female partners should use barrier contraception for one year after administration of Hemgenix.
  - That Hemgenix has a viral vector component, and it may be associated with an increased risk of malignant tumour. Regular liver monitoring for at least 5 years after Hemgenix treatment is needed in patients with preexisting risk factors for hepatocellular carcinoma.
  - Patients should not donate blood, semen, or organs, tissues, and cells for transplantation
- That the patient will get a patient card that should be shown to any doctor or a nurse whenever the patient has a medical appointment.
- The importance to participate in the patients' registry for long-term surveillance of 15 years.

The Patient Card key messages:

- This card is to inform healthcare professionals that the patient has received Hemgenix for Haemophilia B.
- The patient should show the patient card to a doctor or a nurse whenever they have an appointment.
- The patient should seek medical advice for any symptoms suggestive of a thromboembolic event.
- The patient should have regular blood tests and examinations as directed by their doctor.
- The card should warn healthcare professionals that the patient may undergo treatment with corticosteroids for minimising the risk of hepatotoxicity with Hemgenix.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of etranacogene dezaparvovec in adult patients with severe and moderately severe Haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors, the MAH should submit the final analysis report of a study from a registry, according to an agreed protocol.	31 December 2044

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date

In order to confirm the efficacy and safety of etranacogene dezaparvovec in adult patients with severe and moderately severe Haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors, the MAH should submit the final results including 5 years follow-up of the pivotal Study CT-AMT-061-01.	30 June 2024
In order to confirm the efficacy and safety of etranacogene dezaparvovec in adult patients with severe and moderately severe Haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors, the MAH should submit the final results (5 years of data) of pivotal Study CT-AMT-061-02 with 54 subjects.	31 October 2025
In order to confirm the efficacy and safety of etranacogene dezaparvovec in adult patients with severe and moderately severe Haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors, irrespective of baseline anti-AAV5 neutralising antibody titre, the MAH should submit the 1-year follow-up interim analysis report after the first 50 subjects are enrolled in Study CSL222_4001.	31 December 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Hemgenix 1 x 10^{13} genome copies/mL concentrate for solution for infusion
etranacogene dezaparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of etranacogene dezaparvovec contains 1 x 10^{13} genome copies.

3. LIST OF EXCIPIENTS

Excipients: sucrose, polysorbate-20, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium hydrogen phosphate, hydrochloric acid (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

10 mL vial x (number of vials to dose the patient)
Patient-specific pack containing sufficient amount of vials to dose each patient

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only
Read the package leaflet before use.
For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified organisms.
Dispose of in compliance with the local guidance for pharmaceutical waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
D-35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1715/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hemgenix 1 x 10^{13} genome copies/mL sterile concentrate
etranacogene dezaparvovec
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hemgenix 1 x 10^{13} genome copies/mL concentrate for solution for infusion
etranacogene dezaparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.

What is in this leaflet

1. What Hemgenix is and what it is used for

What Hemgenix is and what it is used for

Hemgenix is a gene therapy product that contains the active substance etranacogene dezaparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic defect.

Hemgenix is used for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adults who do not have current or past inhibitors (neutralising antibodies) against the Factor IX protein.

People with Haemophilia B are born with an altered form of a gene needed to make Factor IX, an essential protein required for blood to clot and stop any bleeding. People with Haemophilia B have insufficient levels of Factor IX and are prone to internal or external bleeding episodes.

How Hemgenix works

The active substance in Hemgenix is based on a virus that does not cause disease in humans. This virus has been modified so that it cannot spread in the body but can deliver a copy of the Factor IX gene into the liver cells. This allows the liver to produce the Factor IX protein and raise the levels of working Factor IX in the blood. This helps the blood to clot more normally and prevents or reduces bleeding episodes.

2. What you need to know before you are given Hemgenix

You must not be given Hemgenix

- If you are allergic to etranacogene dezaparvovec or to any of the other ingredients of this medicine (listed in section 6).

- If you suffer from an active infection which is either an acute (short-term) infection, or chronic (long-term) infection that is not controlled by medicines.

- If your liver does not work properly due to advanced liver fibrosis (tissue scarring and thickening), or cirrhosis (scarring due to long-term liver damage).

If any of the above applies to you, or if you are unsure of any of the above, please talk to your doctor before you receive Hemgenix.

Warnings and precautions

Before the treatment with Hemgenix

Your doctor will perform several tests **before** you are given Hemgenix treatment.

Antibody blood tests
Your doctor will conduct blood tests to check for certain antibodies (proteins) before treatment with Hemgenix, including:
- Blood tests to check for the presence of antibodies in your blood directed against the human Factor IX protein (Factor IX inhibitors).
  If you test positive for these antibodies, another test will be performed in approximately 2 weeks. If both the initial test and re-test results are positive, Hemgenix administration will not be initiated.

- Blood tests to check for the amount of antibodies in your blood directed against the type of virus used to make Hemgenix may also be performed.

Liver health
In order to decide if this medicine is suitable for you, your doctor will check the status of your liver health before you start treatment with Hemgenix and perform:
- Blood tests to check the level of liver enzyme in your blood
- Liver ultrasound
- Elastography testing to check for scarring or thickening of your liver.

During or shortly after Hemgenix infusion

Your doctor will monitor you **during or shortly after** Hemgenix infusion.

Infusion-related reactions
Infusion-related side effects can occur during or shortly after you are given the Hemgenix infusion (drip). Your doctor will monitor you during Hemgenix infusion and for at least 3 hours after you are given Hemgenix.

- Symptoms of such side effects are listed in section 4 “Possible side effects”. Tell your doctor or nurse **immediately** if you experience these or any other symptoms during or shortly after the infusion.

- Depending on your symptoms, your infusion may be slowed down or interrupted. If the infusion is interrupted, it can be restarted at a slower rate when the infusion reaction is resolved. Your doctor may also consider if you should be given corticosteroids (e.g. prednisolone or prednisone) to help manage the infusion reaction.

After the treatment with Hemgenix

After treatment with Hemgenix, your doctor will continue to check your health. It is **important** that you **discuss the schedule for these blood** tests with your doctor so that they can be carried out as necessary.

Liver enzymes
Hemgenix will trigger a response within your immune system that could lead to an increased level of certain liver enzymes in your blood called transaminases (transaminitis). Your doctor will regularly monitor your liver enzyme levels to ensure that the medicine is working as it should:

- In the first 3 months, at least, after you are given Hemgenix, you will have blood tests once per week to monitor your liver enzyme levels.
    - If you experience an increase in liver enzymes, you may have more frequent blood tests to check the levels of your liver enzymes, until they return to normal. You may also need to take another medicine (corticosteroids) to manage these side effects.
    - Your doctor may also perform additional tests to exclude other causes for the increase in your liver enzymes, if needed, in consultation with a doctor experienced in liver diseases.
- Your doctor will repeat liver enzyme testing tests every three months from month 4 up to one year after you are given Hemgenix to continue checking of your liver health. In the second year after you are given Hemgenix, your doctor will follow up your liver enzymes half-yearly. After the second year, your doctor will check your liver enzymes annually for at least 5 years after you are given Hemgenix.

Factor IX levels
Your doctor will regularly check your Factor IX levels to see if treatment with Hemgenix was successful.

- In at least the first 3 months after you are given Hemgenix, you will have blood tests once per week to check your Factor IX levels.
- Your doctor will repeat these test every three months from month 4 up to 1 year after you are given Hemgenix to continue checking your Factor IX level. In the second year after you are given Hemgenix, your doctor will check your Factor IX levels half-yearly. Thereafter, your doctor will check them annually at least for 5 years after you are given Hemgenix.
- If you experience an increase in liver enzymes or will need to take another medicine (e.g. corticosteroids), you will have more frequent blood tests to check your Factor IX levels, until your liver enzymes return to normal or you stop taking your additional medicine.

Use of other Haemophilia treatments

After Hemgenix use, talk to your doctor about if or when you should stop your other Haemophilia treatments and develop a treatment plan of what to do in case of surgery, trauma, bleeds, or any procedures that could potentially increase the risk of bleeding. It is very important to continue your monitoring and doctor visits to determine if you need to take other treatments to manage Haemophilia.

Abnormal clotting of blood (thromboembolic events)

After treatment with Hemgenix, your Factor IX protein level may increase. In some patients, it could increase to levels above the normal range for a period of time.

- Unusually elevated Factor IX levels may cause your blood to clot abnormally, increasing the risk of blood clots, such as in the lung (pulmonary thromboembolism) or in a blood vessel of the leg (venous or arterial thrombosis). This theoretical risk is low due to your inborn deficiency in the clotting cascade when compared with healthy subjects.
- You may be at risk of abnormal blood clotting, if you have preexisting problems with your heart and blood vessels (e.g. a history of a heart disease (cardiovascular disease), thick and stiff arteries (arteriosclerosis), high blood pressure (hypertension), or if you are diabetic or above 50 years).

- Your doctor will regularly monitor your blood for any potential abnormalities in Factor IX levels, in particular if you continue receiving your routine Factor IX prophylaxis (Factor IX replacement therapy) after Hemgenix administration (see also section 3 “How to use Hemgenix”).

- Consult your doctor immediately, if you observe signs of abnormal clotting, such as sudden chest pain, shortness of breath, sudden onset of muscle weakness, loss of sensation and/or balance, decreased alertness, difficulty in speaking, or swelling of one or both legs.

Avoiding blood donations and donations for transplantations

The active substance in Hemgenix may temporarily be excreted through your blood, semen, breast milk or bodily waste, a process called shedding (see also section 2 “Pregnancy, breast-feeding and fertility”).

To ensure that people without Haemophilia B are not exposed to Hemgenix DNA through shedding process in your body and/or semen, you will not be able to donate blood, semen, or organs, tissues and cells for transplantation after you have been treated with Hemgenix.

Immunocompromised patients or patients with HIV or other infection

If you have problems with your immune system (are immunocompromised), are undergoing or will undergo a treatment suppressing your immune system, or have an HIV or other new or recent infection, your doctor will decide where you will be able to receive Hemgenix.

Neutralising antibodies against Factor IX proteins (Factor IX inhibitors)

Neutralising antibodies against Factor IX proteins may stop Hemgenix from working properly. Your doctor may check your blood for these antibodies, if your bleeds will not be controlled, or return after you have been given Hemgenix (see also section 3 “How to use Hemgenix”).

Receiving gene therapy again in the future

After receiving Hemgenix, your immune system will produce antibodies to the shell of the AAV vector. It is not yet known whether or under which conditions therapy with Hemgenix may be repeated. It is also not yet known whether or under which conditions subsequent use of another gene therapy may be possible.

Risk of malignancy potentially associated with Hemgenix

- Hemgenix will insert into liver cells and it could possibly insert into the liver cell DNA or the DNA of other body cells. As a consequence, Hemgenix could contribute to a risk of cancer, such as liver cancer (hepatocellular carcinoma). Although there is no evidence of this in the clinical studies so far, this remains possible because of the nature of the medicine. You should therefore discuss this with your physician.

- If you are a patient with preexisting risk factors for hepatocellular carcinoma (e.g. you have liver fibrosis (scarring and thickening of the liver), or Hepatitis B, Hepatitis C, fatty liver (nonalcoholic fatty liver disease (NAFLD)), or you excessively drink alcohol), your doctor will regularly (e.g. annually) monitor your long-term liver health for at least 5 years after Hemgenix administration and perform the following tests:
  - Annual liver ultrasound and
  - Annual blood test to check for increases in so-called alpha-fetoprotein.

- After treatment with Hemgenix, you will be expected to enrol in a follow up study to help study the long-term safety of the treatment for 15 years, how well it continues to work and any side effects

that may be linked to the treatment. In the event of cancer, your doctor may take a sample of your cancer (biopsy) to check if Hemgenix has inserted into the cell DNA.

Children and adolescents

Hemgenix has not been studied in children or adolescents under the age of 18.

Other medicines and Hemgenix

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

If you are taking medication that are known to damage the liver (hepatotoxic medication), your doctor may decide that you may need to stop this medication to be able to receive Hemgenix.

Pregnancy, breast-feeding and fertility

There are no data regarding Hemgenix use in women with Haemophilia B.

If you are pregnant or breast-feeding, think you may be pregnant or plan to become pregnant, ask your doctor for advice prior to be given Hemgenix.

- Hemgenix treatment is not recommended in women who are able to become pregnant. It is not yet known whether Hemgenix can be used safely in these patients as the effects on pregnancy and the unborn child are not known.

- Hemgenix should not be used during pregnancy. It is not known whether this medicinal product can cause harm to your unborn baby when administered to you during your pregnancy.

- Hemgenix should not be used during breast-feeding. It is unknown whether this medicine is excreted in human milk. A risk to the newborns/infants cannot be excluded.

Use of contraception and avoiding partner pregnancy for a period of time

After a male patient has been treated with Hemgenix, the patient and any female partner must avoid pregnancy for 12 months. You should use effective contraception (e.g. barrier contraception such as condom or diaphragm). This is to prevent the theoretical risk that the Factor IX gene from a father's Hemgenix treatment is transmitted to a child with unknown consequences. For the same reason, male patients must not donate semen. Discuss with your doctor which methods of contraception are suitable.

Driving and using machines

Hemgenix has minor influence on the ability to drive and use machines. Temporary dizziness, tiredness, and headaches have occurred shortly after Hemgenix infusion. If you are affected, you should use caution until you are certain that Hemgenix does not adversely affect your ability to drive or use machines. Talk to your doctor about this.

Hemgenix contains sodium and potassium

- The medicine contains 35.2 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.8% of the recommended maximum daily dietary intake of sodium for an adult.

- This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, that is to say essentially potassium-free.

3. How Hemgenix is given

Hemgenix will be given to you in a hospital setting under direction of a doctor experienced and trained in the treatment of your condition Haemophilia B.

Hemgenix will be given to you **only once** by a single slow infusion (drip) into a vein. The infusion will take usually 1 to 2 hours to be completed.

Your doctor will work out the correct dose for you, based on your body weight.

Discontinuation of exogenous Factor IX treatment

- It may take several weeks before improved bleeding control becomes apparent after Hemgenix infusion, and you may need to continue your replacement therapy with exogenous Factor IX during the first weeks after Hemgenix infusion.

- Your doctor will regularly monitor your blood for the Factor IX activity levels, i.e. weekly for at least first 3 months, and at regular intervals thereafter, and decide if and when you should receive, reduce, or stop your exogenous Factor IX therapy (see section 2).

If you have any questions on the use of Hemgenix ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects were observed in clinical studies with Hemgenix.

Very Common (may occur with more than 1 in 10 patients)
- Headache
- Increased levels of liver enzymes in the blood (Alanine aminotransferase increased)
- Increased levels of liver enzymes in the blood (Aspartate aminotransferase increased)
- Flu-like illness (Influenza-like illness)
- Increased levels of C-reactive protein, a marker of inflammation
- Infusion related reaction (allergic reactions (hypersensitivity), infusion site reaction, dizziness, eye itching (pruritus), reddening of the skin (flushing), upper tummy (abdominal) pain, itchy rash (urticaria), chest discomfort, and fever)

Common (may occur with up to 1 in 10 patients)
- Dizziness
- Feeling sick (Nausea)
- Tiredness (Fatigue)
- Feeling generally unwell (Malaise)
- Increased blood levels of bilirubin, a yellow breakdown substance of the red blood cells
- Increased blood levels of creatine phosphokinase, an enzyme (protein) found mainly in the heart, brain and skeletal muscle

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hemgenix

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP.

Store in a refrigerator (2 °C - 8 °C). Do not freeze.
Store vials in the original package in order to protect from light.

Dilute before use.
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, Hemgenix can be stored at 15 °C - 25 °C in the infusion bag protected from light for up to 24 hours after the dose preparation.

Do not use this medicine if you notice particles, cloudiness or discolouration.

6. Contents of the pack and other information

What Hemgenix contains

- The active substance is etranacogene dezaparvovec. Each mL of etranacogene dezaparvovec contains 1 x 10^{13} gene copies (gc)/mL.

- The other ingredients (excipients) are sucrose, polysorbate-20, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium hydrogen phosphate, hydrochloric acid (for pH adjustment), water for injections (see also section 2 ”Hemgenix contains sodium and potassium.”).

This medicine contains genetically modified organisms.

What Hemgenix looks like and contents of the pack

Hemgenix is a concentrate for solution for infusion (sterile concentrate).

Hemgenix is a clear, colourless solution.

Hemgenix is supplied in a vial containing 10 mL of etranacogene dezaparvovec.

The total number of vials in a pack, corresponds to the dosing requirement for individual patient depending on his body weight, and is provided on the package.

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms (GMOs).

Personal protective equipment, including gloves, safety goggles, protective clothing and masks, should be worn while preparing and administering etranacogene dezaparvovec.

Preparation of etranacogene dezaparvovec prior to administration

1. Use aseptic techniques during the preparation and administration of etranacogene dezaparvovec.
2. Use etranacogene dezaparvovec vial(s) only once (single-use vial(s)).
3. Verify the required dose of etranacogene dezaparvovec based on the patient's body weight. The total number of vials in each finished pack corresponds to the dosing requirement for each individual patient based on the body weight.
4. Etranacogene dezaparvovec must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration.
    - Withdraw the volume of the calculated Hemgenix dose (in mL) from the 500 mL-infusion bag(s) with sodium chloride 9 mg/mL (0.9%) solution for injection. The volume to be withdrawn will vary based on the patient body weight.
        - For patients <120 kg body weight, withdraw the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from one 500 mL-infusion bag.
        - For patients ≥120 kg body weight, withdrawn the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from two 500 mL-infusion bags, by withdrawing half of the volume from each of the two 500 mL-infusion bags.
    - Add subsequently the required Hemgenix dose to the infusion bag(s) to bring the total volume in each infusion bag back to 500 mL.
5. Add the Hemgenix dose directly into the sodium chloride 9 mg/mL (0.9%) solution for injection. Do not add the Hemgenix dose into the air within the infusion bag during diluting.
6. Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
7. To avoid foaming:

- Do not shake the etranacogene dezaparvovec vial(s) and the prepared infusion bag(s).
- Do not use filter needles during preparation of etranacogene dezaparvovec.

8. To reduce the risk of spillage and/or aerosol formation, the infusion bag(s) should be provided connected to an infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
9. The infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be connected to the main intravenous infusion line also primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection prior to use.
10. Use only sodium chloride 9 mg/mL (0.9%) solution for injection since the stability of etranacogene dezaparvovec has not been determined with other solutions and diluents.
11. Do not infuse the diluted etranacogene dezaparvovec solution in the same intravenous line with any other products.
12. Do not use a central line or port.

Administration

13. Diluted etranacogene dezaparvovec should be visually inspected prior to administration. The diluted etranacogene dezaparvovec should be a clear, colourless solution. If particulates, cloudiness or discoloration are visible in the infusion bag, do not use etranacogene dezaparvovec.
14. Use the product after dilution as soon as possible. You must not exceed the storage time of the diluted product beyond that provided in SmPC section 6.3.
15. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES).
16. The diluted etranacogene dezaparvovec solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
17. Etranacogene dezaparvovec solution should be infused closely following the infusion rate(s) provided in SmPC section 4.2. The administration should be completed within ≤24 hours after the dose preparation (see SmPC section 4.2).
18. After the entire content of the infusion bag(s) is infused, the infusion line must be flushed at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure all etranacogene dezaparvovec is delivered.

Measures to take in case of accidental exposure

In case of accidental exposure local guidance for pharmaceutical waste must be followed.

- In case of accidental exposure to eyes, immediately flush eyes with water for at least 15 minutes. Do not use alcohol solution.
- In case of accidental needle stick exposure, encourage bleeding of the wound and wash injection area well with soap and water.
- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. Do not use alcohol solution.
- In case of accidental inhalation, move the person into fresh air.
- In case of accidental oral exposure, abundantly rinse mouth with water.
- In each case, obtain subsequently medical attention.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable material that may have come in contact with Hemgenix (solid and liquid waste) must be disposed of in compliance with the local guidance for pharmaceutical waste. The risk of an adverse effect to human health upon accidental exposure to Hemgenix and the environmental risks are, however, considered negligible.
Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during Hemgenix use.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage and then autoclaved, if possible.