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

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.

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 pre-existing 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. Etrancogene 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 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 (see section 4.4).

- 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 pre-existing neutralising anti-AAV5 antibodies.

Pre-existing neutralising anti-AAV5 antibodies above a titre of 1:898, based on the neutralising anti-AAV5 antibody assay with extended measuring range (equivalent to 1:678 titre based on the previous clinical study assay), may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of Hemgenix therapy (see section 5.1).

There is limited data in patients with neutralising anti-AAV5 antibodies above 1:898 (equivalent to the 1:678 titre based on the clinical study assay). In the clinical studies

with etranacogene dezaparvovec, in 1 patient with a pre-existing neutralising anti-AAV5 antibody titre of 1:3212 (tested using the clinical study assay equivalent to 1:4417 titre based on the neutralising anti-AAV5 antibody assay with extended measuring range), 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 pre-existing neutralising anti-AAV5 antibodies up to a titre of 1:678 (tested using the clinical study assay, equivalent to 1:898 titre based on the neutralising anti-AAV5 antibody assay with extended measuring range), mean Factor IX activity levels were within the same range but numerically lower compared to those of the patient sub-group without detectable pre-existing neutralising anti-AAV5 antibodies. However, both patient groups, with and without detectable pre-existing 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 assessed and liver ultrasound and elastography performed, along with laboratory tests to evaluate for active Hepatitis B and C. 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). In patients with active Hepatitis B or C, etranacogene dezaparvovec treatment must be postponed until the infection is no longer active (see section 4.3).

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 pre-existing 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 or Hepatitis C). 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 pre-existing 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 safety of etranacogene dezaparvovec was evaluated in clinical studies involving 57 adult patients, who received a single intravenous dose of etranacogene dezaparvovec and were followed up for a period of 5 years (see section 5.1). The Table 3 shows the overview of the ADRs from the clinical trials with etranacogene dezaparvovec. 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	Influenza like illness	Very common
	Fatigue, malaise	Common
Investigations	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%) within 24 hours post-dose.

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[f]**
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
[f]Adverse event data are derived from patients followed for up to two years post-dose.

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).

Treatment-emergent 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 (see section 4.4). 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 (range: 51 to 130). 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. After month 6 post-dose, no persistence of treatment-related transaminitis was observed and no steroid treatment was required.
No delayed hepatotoxicity was observed (see section 4.4).

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, as tested using the clinical study assay, by week 3 post-dose and remained elevated above the upper limit of quantification, as measured up to the end of the study (see section 5.1)

Reporting of suspected adverse reactions
Reporting suspected adverse 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 UK Yellow Card Scheme at http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

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

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 were followed up for 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 regular 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 for the primary analysis. Fifty patients completed the full 5-year follow-up.

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 regular Factor IX prophylaxis (see Table 5). The ABR reduction for all types of bleeds was maintained through 5 years post-dose (see Table 5 and 6).

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)**	**7-60 months post-dose FAS (N=54)**	**≥6-month lead-in period (N=53)*** **	**7-18 months post-dose (N=53)*** **	**7-60 months post-dose (N=53)*** **
Number of patients with bleeds	40 (74.1%)	20 (37.0%)	34 (63.0%)	40 (75.5%)	19 (35.8%)	33 (62.3%)
Number of patients with zero bleeds	14 (25.9%)	34 (63.0%)	20 (37%)	13 (24.5%)	34 (64.2%)	20 (37%)
Number of any bleeds	136	54	151	136	49	146
Number of person years for bleeding events	33.12	49.78	219.11			219.10
Adjusted* ABR**	4.19 (3.22,	1.51 (0.81,	1.52 (0.72,	3.89 (2.93,	1.07 (0.63,	0.96 (0.53,

(95% CI) for any bleeds	5.45)	2.82)	3.26)	5.16)	1.82)	1.76)
ABR reduction (lead-in to post-treatment) 2-sided 95% Wald CI 1-sided p-value****	-	64% (36%, 80%) 0.0002	63% (24%, 82%) p=0.0035		72% (57%,83%) p<0.0001	75% (46%, 87%) 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	0.53 p=0.0133	-	-	-
Adjusted ABR for joint bleeds 1-sided p-value	2.35	0.51 p<0.0001	0.35 p<0.0001	-	-	-
Adjusted ABR for traumatic bleeds 1-sided p-value	2.09	0.62 p<0.0001	0.43 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 or month 60, respectively, 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 (tested using the clinical study assay, equivalent to 1:4417 titre based on the neutralising anti-AAV5 antibody assay with extended measuring range) who did not respond to treatment, i.e., did not show Factor IX expression and activity post-dose.

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

[i]The severity of a bleeding episode was assessed by the subject (subject-reported).

Table 6. Total bleeding events and ABRs by year (FAS)

	≥6-month Lead-in period (N=54)	**Year 1 (N=54)**	**Year 2 (N=54)**	**Year 3 (N=53[i])**	**Year 4 (N=51[ii])**	**Year 5 (N=51[ii])**
Patients with bleeds	40 (74.1%)	23 (42.6%)	21 (38.9%)	14 (26.4%)	15 (29.4%)	12 (23.5%)
Patients with zero bleeds	14 (25.9%)	31 (57.4%)	33 (61.1%)	39 (73.6%)	36 (70.6%)	39 (76.5%)
Any bleeds	136	55	48	37	22	18
Adjusted[*] ABR (95% CI) for any bleeds	4.19 3.22, 5.45	1.33 0.84, 2.13	0.91 0.53, 1.56	0.83 0.39, 1.74	0.40 0.24, 0.67	0.40 0.23, 0.71
ABR reduction (lead-in to post-treatment) 2-sided 95% Wald CI 1-sided p-value[**]	-	66% 46%, 79% p<0.0001	78% 65%, 86% p<0.0001	80% 57%, 90% p<0.0001	90% 83%, 94% p<0.0001	90% 82%, 94% 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.)

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

[i]The population data includes all patients dosed except for 1 patient who died at month 15 due to an unrelated concomitant disease.

[ii]The population data includes all patients dosed except for 1 patient who died at month 15 due to an unrelated concomitant disease; 1 patient who withdrew consent and discontinued; 1 patient who underwent a liver transplantation due to unrelated concomitant disease.

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 7). 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 7. Uncontaminated [2] Factor IX activity at 6, 12, 24 and 60 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]**	**24 months post-dose[5] (N=50)[2]**	**60 months post-dose[5] (N=48)[2]**
Mean % (SD)	1.19 (0.39)	38.95 (18.72)	41.48 (21.71)	36.66 (18.96)	36.09 (15.68)
Median % (min, max)	1.0 (1.0, 2.0)	37.30 (8.2, 97.1)	39.90 (5.9, 113.0)	33.85 (4.7, 99.2)	35.45 (5.5, 74.5)
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	34.13 (2.325) 29.57, 38.69 p<0.0001	33.98 (2.213) 29.63, 38.32 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, 2 patients who died at month 15 and month 55 post-dose, respectively, due to an unrelated concomitant disease, 1 patient with 1:3212 titre of preexisting neutralising anti-AAV5 antibodies (tested using the clinical study assay, equivalent to 1:4417 titre based on the neutralising anti-AAV5 antibody assay with extended measuring range) who did not respond to treatment, and 1 patient who underwent a liver transplantation due to unrelated concomitant

disease, and 2 patients with contamination with exogenous Factor IX. Accordingly, the population data included 54 to 47 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 and 60, 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 activity levels from 6 months through the end of the study in 49 of the 50 patients who completed the study (see section 5.1). 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 8 years (see section 5.3). In the phase 2b study, Factor IX activity levels achieved after etranacogene dezaparvovec treatment in all 3 enrolled patients remained stable from 6 months through the end of the study, as measured at 5 years post-dose.

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 8). In 1 patient with a titre of 1:3212 for preexisting anti-AAV5 antibodies at screening (tested using the clinical study assay, equivalent to 1:4417 titre based on the neutralising anti-AAV5 antibody assay with extended measuring range), no response to etranacogene dezaparvovec treatment was observed, with no Factor IX expression and activity.

Table 8. 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 patients [#]	**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.

				Change from Baseline		
	Number of patients [#]	**Mean Factor IX activity (%) (SD)**	**Median Factor IX activity (%) (min, max)**	**Least Squares mean (SE)** [†]	**95% CI**	**1-sided p-value**
Month 6	18	35.91 (19.02)	35.60 (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 24	17	32.98 (18.51)	33.50 (9.1, 88.3)	28.35 (3.928)	20.62, 36.08	<0.0001
Month 60	15	30.34 (14.54)	30.90 (8.0, 57.1)	26.73 (4.080)	18.71, 34.75	<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 24	33	38.55 (19.19)	35.40 (4.7, 99.2)	37.40 (2.933)	31.64, 43.16	<0.0001
Month 60	33	38.71 (15.68)	36.40 (5.0, 74.5)	37.56 (2.776)	32.11, 43.01	<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.

[#]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, 2 patients who died at month 15 and 55, respectively, post-dose due to unrelated concomitant disease, 1 patient who did not respond to treatment, 2 patients with contamination with exogenous Factor IX, and 1 patient with liver transplantation due to unrelated concomitant disease. Accordingly, the population data included 54 to 47 patients with uncontaminated sampling.

The study also demonstrated superiority of etranacogene dezaparvovec at 18-months post-dose over the regular exogenous Factor IX prophylaxis in the lead-

in period (see Table 9). The ABR for Factor IX-treated bleeding episodes during the month 7 to 18 post-dose period was reduced by 77% (see Table 9).

Table 9. 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)**	**7-60 months post-dose FAS (N=54)**
Number of patients with Factor IX-treated bleeds	37 (68.5%)	15 (27.8%)	24 (44.4%)
Number of Factor IX-treated bleeds	118	30	96
Adjusted ABR (95% CI) for Factor IX-treated bleeds	3.65 (2.82, 4.74)	0.84 (0.41, 1.73)	1.82 (0.64, 5.19)
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	0.5 (0.18, 1.40) p<0.0943
Adjusted ABR (95% CI) for spontaneous bleeds treated with Factor IX	1.34 (0.87, 2.06)	0.45 (0.15, 1.39)	0.53 (0.20, 1.37)
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	0.35 (0.13, 0.88) p=0.0133
Adjusted ABR (95% CI) for joint bleeds treated with Factor IX	2.13 (1.58, 2.88)	0.44 (0.19, 1.00)	0.35 (0.18, 0.68)
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	0.15 (0.08, 0.28) p<0.0001

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

During the month 7 to 60 post-treatment, the ABR for Factor IX-treated bleeding episodes remained reduced by 50% in comparison to lead-in period (see Table 9).

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 regular 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 regular Factor IX prophylaxis. Between

month 24 and 60, one patient returned to regular continuous Factor IX prophylaxis. Of 54 patients, 51 (94.4.%) remained free from regular continuous Factor IX prophylaxis from day 21 through the remainder follow-up period, demonstrating a durable therapeutic effect with reduced treatment burden.

Overall, similar results were observed at 24 and 60 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 5 years post-dose. Similarly, none of the 3 patients enrolled in the phase 2b study showed evidence of neutralising inhibitors over the period of 5 years post-dose. The 3 patients demonstrated clinically relevant increases in Factor IX activity and discontinued their regular Factor IX replacement prophylaxis over the period of 5 years post-dose.

Paediatric population

The Licensing Authority 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 and the Medicines and Healthcare products Regulatory 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 quantitative 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 infectious 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. Several subjects did not return the required number of blood and semen samples to assess the shedding status as per the definition (n = 9, including 2 patients with no samples). Considering shedding results obtained from the final 2 available consecutive samples, while accounting for missing 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. At month 60, clearance of vector DNA, as per the definition and considering for missing samples, was confirmed in 90.7% (49/54) of patients in blood and in 83.3% (45/54) of patients in semen.
The median time to absence of shedding was 52.6 weeks in blood and 43.7 weeks in semen at 60 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 . 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. Do not expose etranacogene dezaparvovec to the light of an ultraviolet radiation disinfection lamp.
3. Use etranacogene dezaparvovec vial(s) only once (single-use vial(s)).
4. 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.

Example calculation for 72 kg patient:

Patient body weight	Etranacogene dezaparvovec dose (mL) = body weight × 2	Number of vials* needed = Etranacogene dezaparvovec dose (mL) divided by 10, then rounded up to the nearest whole number of vials
72 kg	144 mL	15

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

The patient body weight used for the dose calculation should be taken to the nearest full kilogram.

Example:
For a patient weighing between 72.1 kg to 72.4 kg use 72 kg.
For a patient weighing between 72.5 kg to 72.9 kg use 73 kg.

5. Etranacogene dezaparvovec must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration.
   - Prior to dilution, inspect each of the etranacogene dezaparvovec vials.
     - If particulates, cloudiness, or discoloration is visible, do not use the vial(s).
   - Gently swirl the vials 3 times (about 10 seconds) to homogenize the etranacogene dezaparvovec suspension.
     - To avoid foaming, do not shake the etranacogene dezaparvovec vial(s).
   - 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.
   - Withdraw etranacogene dezaparvovec from each vial using a 20 G needle and syringe.
   - 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.
6. 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.
7. Gently invert the infusion bag(s) at least 3 times (about 10 seconds) to mix the solution and ensure even distribution of the diluted product.
8. To avoid foaming:
   - Do not shake the prepared infusion bag(s).
   - Do not use filter needles during preparation of etranacogene dezaparvovec.
9. 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.
10. 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.
11. 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.
12. Do not infuse the diluted etranacogene dezaparvovec solution in the same intravenous line with any other products.
13. Do not use a central line or port.

<u>Administration</u>

14. 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.
15. 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.
16. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES).
17. The diluted etranacogene dezaparvovec solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
18. 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).
19. 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

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Germany

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