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

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Fidanacogene elaparvovec is a gene therapy medicinal product that consists of a recombinant viral capsid derived from a naturally occurring adeno-associated viral serotype Rh74 (AAVRh74var) packaging genome containing the human coagulation factor IX (FIX) transgene modified to be a high factor IX activity (Padua) variant known as FIX-R338L.

Fidanacogene elaparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each mL of fidanacogene elaparvovec contains 0.79 - 1.21 × 10^{13} vector genomes (vg).

Each vial contains an extractable volume of 1 mL.

The quantitative information regarding actual concentration, and patient dose calculation is provided in the Lot Information Sheet (LIS) accompanying the medicinal product for treatment.

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

Excipient with known effect

This medicinal product contains 4.55 mg sodium per vial.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

A clear to slightly opalescent, colourless to slightly brown solution with a pH of 6.8 - 7.8 and an osmolarity of approximately 348 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BEQVEZ 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 and without detectable antibodies to variant AAV serotype Rh74.

4.2 Posology and method of administration

Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. It is recommended that this medicinal product is administered in a setting where personnel and equipment are available to treat possible infusion-related reactions (see section 4.4).

A prophylactic dose of factor IX replacement should be given prior to fidanacogene elaparvovec infusion (see section 4.4).

Patient selection

Eligibility for treatment should be confirmed within 8 weeks prior to infusion by the following test results:

- negative for AAVRh74var pre-existing antibodies should be assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.
- absence of clinically significant liver disease (see sections 4.3 and 4.4).
- negative for factor IX inhibitors by history and test < 0.6 Bethesda Units (BU).
- absence of active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as active chronic hepatitis B, hepatitis C, or human immunodeficiency virus infection [HIV]) (see section 4.3).

Posology

The recommended dose of BEQVEZ is a single-dose of 5×10^{11} vector genomes per kg (vg/kg) of body weight.

To determine the patient's dose, the following calculation steps are needed:

Calculation of patient's dose weight
The dose of BEQVEZ is based on the patient's body mass index (BMI) in kg/m^2.

Table 1. Patient's dose weight adjustment according to BMI

Patient's BMI	Patient's dose weight (kg) adjustment
≤ 30 kg/m^2	Dose weight = Actual body weight
> 30 kg/m^2	Determine using the following calculation: Dose weight (kg) = 30 kg/m^2 × [Height (m)]^2

Note:
- The intermediate calculation of height (m^2) should NOT be rounded.
- Dose weight should be rounded to 1 decimal place.

Calculation of patient's dose volume in millilitres (mL)
Patient's dose weight in kilograms (kg) × target dose per kilogram (5×10^{11} vg/kg) = dose in vg to be administered

Dose in vg to be administered ÷ Actual concentration (vg/mL)* = patient's dose volume in mL

*See the accompanying LIS for information pertaining to the actual concentration of vg per vial.

Special populations

Hepatic impairment
The safety and efficacy of fidanacogene elaparvovec in patients with severe hepatic impairment have not been studied. Fidanacogene elaparvovec is contraindicated in patients with advanced hepatic fibrosis or advanced hepatic cirrhosis (see section 4.3), and not recommended for use in patients with other significant hepatobiliary disorders (see section 4.4).

Patients who are HCV positive /HBV positive /HIV positive
No dose adjustment is needed in patients who are hepatitis C virus (HCV) positive, hepatitis B virus (HBV) positive and/or human immunodeficiency virus (HIV) positive. Limited data are available in patients with controlled HIV infections and a past medical history of active HCV and HBV (see sections 4.3 and 4.4).

Renal impairment
No dose adjustment is needed in patients with renal impairment. The safety and efficacy of BEQVEZ have not been studied in patients with clinically relevant renal impairment (creatinine > 2.0 mg/dL).

Elderly
The safety and efficacy of fidanacogene elaparvovec in patients ≥ 65 years old have not been established. No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of fidanacogene elaparvovec in children and adolescents under 18 years of age have not yet been established. No data are available.

Method of administration

For intravenous use after dilution.

BEQVEZ is administered as a single-dose intravenous infusion over approximately 60 minutes in an appropriate infusion volume (see section 6.6).

Do not infuse as an intravenous push or bolus. 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).

Before administration, it must be confirmed that the patient's identity matches the unique patient information (i.e., lot number) on the vials, inner cartons, outer cartons, and accompanying documentation. The total number of vials to be administered must also be confirmed with the patient-specific information on the LIS.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of medicinal product, 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).

Advanced hepatic fibrosis or advanced hepatic 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.

Pre-existing immunity against AAVRh74var

Anti-AAVRh74var antibody formation can take place after exposure to a virus very similar to the modified virus. Before administration, the absence of antibodies to AAVRh74var must be demonstrated using an appropriately validated assay (see sections 4.1 and 4.2). It is recommended that patients should be dosed as close as possible (e.g., within 8 weeks) following antibody testing confirming the absence of anti-AAVRh74var antibodies.

Pre-treatment evaluation of hepatobiliary condition

Pre-treatment evaluation of hepatobiliary condition should confirm the absence of clinically significant hepatobiliary disease, as defined by any of the below:

- alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) levels > 2 × upper limit of normal (ULN), bearing in mind that at least 2 readings may be required to interpret variability over time (at most within 4 weeks)
- bilirubin > 1.5 × ULN (at most within 4 weeks)
- current liver-related coagulopathy, hypoalbuminemia, persistent jaundice, cirrhosis, active viral hepatitis
- history of portal hypertension, splenomegaly, or hepatic encephalopathy
- negative fibrosis assessment (at most 3 months before infusion)

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 BEQVEZ administration.

Patients with active infections, either acute or uncontrolled chronic

There is no clinical experience with administration of fidanacogene elaparvovec 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 fidanacogene elaparvovec and reduce its efficacy and/or cause adverse reactions. In patients with such infections, fidanacogene elaparvovec treatment is contraindicated (see section 4.3). If there are signs or symptoms of acute or uncontrolled chronic active infections, fidanacogene elaparvovec treatment must be postponed until the infection has resolved or is controlled.

Limited clinical data are available in patients with controlled HIV infection treated with fidanacogene elaparvovec.

Infusion-related reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, are possible during or shortly after fidanacogene elaparvovec infusion. 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 should be closely adhered to, in order to ensure patient tolerability. Suspicion of an infusion reaction requires slowing or immediate stopping of the infusion (see section 4.2). Based on

clinical judgement, management of infusion reactions should be done according to guidelines for management of allergic reactions, including the discontinuation and/or the administration of appropriate treatment.

To minimise the risk of acute hypersensitivity reactions, patients should be closely monitored for clinical signs and symptoms of infusion reactions and acute or delayed hypersensitivity reactions. Patients should be informed of the early symptoms and signs of hypersensitivity reactions and should be advised to contact their physician and/or seek immediate emergency care if they experience an infusion-related reaction.

Discontinuation of factor IX concentrates

Following fidanacogene elaparvovec infusion, patients should discontinue prophylaxis once the endogenous FIX:C activity levels are considered sufficient to prevent spontaneous bleeding.

Monitoring of factor IX activity and hepatic function

Following administration of fidanacogene elaparvovec, patients can develop transient and asymptomatic elevation of transaminases (see section 4.8). Although the exact aetiology of elevations has not yet been established, it is believed that immune-mediated elevations in liver function tests (LFTs) are the result of an AAV capsid triggered response with subsequent hepatocyte lysis and inflammation.

ALT/AST and factor IX activity levels should be monitored following the administration of fidanacogene elaparvovec (see Table 2). Monitoring of creatine phosphokinase (CPK) is recommended to evaluate for alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise). Corticosteroid treatment should be instituted in response to aminotransferase elevations to control hepatic reactions and prevent or mitigate a potential reduction in transgene expression (see Table 3 and Table 4).

During the first six months after BEQVEZ administration, the purpose of hepatic and factor IX monitoring is to detect increases in transaminases which may be suggestive of or accompanied by decreased factor IX activity and may indicate the need to initiate corticosteroid treatment. Following the first 6 months post-BEQVEZ administration, hepatic and factor IX monitoring is intended to assess liver health and bleeding risk.

Table 2. Recommended hepatic function (ALT and AST) and factor IX activity monitoring*

Timeframe	Monitoring frequency[a]
Weeks 1 to 12	Once or twice weekly
Weeks 13 to 18	Weekly
Weeks 19 to 52 (end of year 1)	At weeks 24, 32, 42 and 52
Year 2 to end of year 3[b]	Quarterly
Year 4 to end of year 6	Twice yearly
After year 6	Annually

* It is recommended where possible to use the same laboratory for monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

[a] Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering. Adjustment of the monitoring frequency may also be indicated depending on the individual patient situation.

[b] Starting at week 65

Variability of tests for factor IX activity

In regards to factor IX activity monitoring, results from a field study indicate inter-laboratory variability across the different one-stage reagents used in the study, with more variability at the lower levels (0.025 IU/mL). These results support prior data that demonstrated differences in factor IX

activity from transgene-derived FIX-R338L variant in different one-stage assays and chromogenic assays, with consistently higher factor IX activity observed for the silica-based one-stage assays.

It is recommended where possible to use the same laboratory (chromogenic or one-stage assays) for factor IX activity monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

Based on an in vitro study, transgene FIX-R338L variant protein in fidanacogene elaparvovec participants' plasma samples did not interfere with the detection of FIX activity from plasma derived, recombinant, or recombinant extended-half-life FIX products which were spiked into the plasma samples and assessed with two one-stage (OS) assays (Actin FSL and SynthASil) as well as a chromogenic assay using Rox FIX. Glycol-pegylated recombinant FIX products were not assessed in the study. It is suggested not to use silica-based activated partial thromboplastin time (aPTT) assay for the measurement of FIX:C in presence of (recombinant) FIX products; the respective product information for monitoring guidance when using (recombinant) FIX products should be referred to.

Initiation and use of corticosteroids

Corticosteroid treatment should be initiated if aminotransferase elevations are observed or decrease in the activity of factor IX is observed to maintain the transgene expression by transduced hepatocytes (see Table 3 and Table 4). There is limited information with regards to the benefit of starting a new corticosteroid course after the first 6 months of BEQVEZ administration.

Table 3 gives the recommended tapering course of oral corticosteroids (i.e., prednisone/prednisolone) which will be the first consideration for suppression of hepatic laboratory abnormalities. Reference to the corticosteroid product information for risks and required precautions is recommended. In the absence of alternative aetiology, treatment with corticosteroids for vector induced hepatitis would be highly recommended if any of the following criteria are met:

Transaminase increase (ALT and AST)

- Transaminase value 2 × ULN or single increase ≥ 1.5-fold since the last value obtained prior to infusion (see section 4.2).
- Consecutive increases.

Factor IX activity decrease

- A single significant decrease that could trigger the risk of bleeding, not associated with a recent infusion of external factor IX product or factor IX inhibitor.
- Consecutive decreases if occurring during the first 120 days post-infusion.

Table 3. Recommended treatment regimen for oral corticosteroids

Schedule (oral corticosteroid treatment regimen)	**Prednisolone/prednisone (mg/day)**
Week 1	~60 to 100 according to body weight
Week 2	60*
Week 3	40
Week 4	30
Week 5	30
Maintenance dose until ALT/AST return to baseline level	20
Taper dose after baseline level has been reached	Reduce by 5 mg/day until 10 mg/day is achieved then reduce by 2.5 mg/week up to 5 mg daily.

* The subsequent prednisolone/prednisone taper should not be started until the ALT and/or AST have declined for at least 2 consecutive lab draws or have returned to approximately baseline (pre administration) levels and any decline in factor IX activity has plateaued.

If there is no evidence of resolution of transaminase elevation or in the decrease in activity of factor IX after the first week of oral corticosteroid treatment, consider to use a combination of intravenous methylprednisolone and oral corticosteroids and a hepatologist should be consulted as required (see Table 4).

Table 4. Recommended treatment regimen for combination intravenous and oral corticosteroids

Schedule (corticosteroid treatment regimen)	Oral prednisolone/prednisone (mg/day)	Intravenous methylprednisolone (mg/day)
Days 1* to 3	Not applicable (n/a)	1 000
Days 4 to 7	20	n/a
Week 2	60	n/a
Week 3	60	n/a
Week 4	40	n/a
Week 5	30	n/a
Week 6	30	n/a
Week 7	20	n/a
Week 8	10	n/a
Week 9	5	n/a

* Day 1 of treatment escalation

Monitoring for factor IX inhibitor development

No clinical data is available in patients with detectable factor IX inhibitors treated with fidanacogene elaparvovec. BEQVEZ is not indicated for use in patients with a history of factor IX inhibitors (see section 4.1).

Patients should be monitored through appropriate clinical observations and laboratory tests for the development of inhibitors to factor IX after BEQVEZ administration. An assay that detects factor IX inhibitors if bleeding is not controlled, or plasma factor IX activity levels decrease, should be performed.

Risk of malignancy in relation to vector integration in the DNA of body cells

As there is a theoretical risk of malignant transformation leading to cancer resulting from AAV-mediated integration into the host cell DNA, considerations should be given to regular long-term follow-up monitoring (see long-term follow-up).

It is recommended that patients with pre-existing 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 on a yearly basis for at least 5 years after BEQVEZ administration (see section 4.3).

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.

Measures in relation to transgene DNA shedding

Male patients should be informed on the need for contraceptive measures for them or their female partners of childbearing potential. BEQVEZ is not recommended in women of childbearing potential (see section 4.6).

BEQVEZ may be transmitted to persons other than the patient receiving the treatment through patient excretions and secretions (see section 5.2). Temporary vector shedding of intravenously administered AAV-based gene therapies occurs primarily through urine, and to some extent saliva, and mucus.

To minimise the risk of transmission to other persons, patients should be instructed regarding proper hand hygiene when coming into direct contact with patient secretions or excretions.

These precautions should be followed for 6 months after BEQVEZ infusion, especially in the case of pregnancy or immunodeficiency of close contacts.

Risk of thromboembolic events

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 after treatment.

Patients should be evaluated before and after administration of fidanacogene elaparvovec for risk factors for thrombosis and general cardiovascular risk factors. Based on factor IX activity levels achieved, patients should be advised according to their individual condition. Patients should seek immediate medical attention if they observe signs or symptoms that may indicate a thrombotic event.

Immunocompromised patients

No immunocompromised patients, including patients undergoing immunosuppressive treatment within 30 days before fidanacogene elaparvovec infusion, were enrolled in clinical studies with fidanacogene elaparvovec.

Safety and efficacy of this medicinal product in these patients have not been established. Use in immunocompromised patients is based on healthcare professional's judgement, taking into account the patient's general health and potential for corticosteroid use post-fidanacogene elaparvovec treatment.

Use of factor IX concentrates or haemostatic agents after treatment with fidanacogene elaparvovec

Following administration of fidanacogene elaparvovec:

- Factor IX concentrates/haemostatic agents may be used in the management of the perioperative setting and in case of invasive procedures, surgery, trauma, or bleeds, in accordance 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 ≤ 2 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.

When monitoring a patient's haemostatic activity, please refer to section 4.4 for laboratory tests following infusion of BEQVEZ.

Repeated treatment and impact to other AAV-mediated therapies

It is not yet known whether or under what conditions fidanacogene elaparvovec 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.

Blood, organ, tissue and cell donation

Patients treated with this medicinal product should not donate blood, organs, tissue and cells for transplantation. This information is provided in the Patient Card which should be given to the patient after treatment.

Long-term follow-up

Patients are expected to be enrolled in a registry to follow haemophilia patients for 15 years after infusion, to better understand the long-term safety and efficacy of this gene therapy.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.

BEQVEZ will be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Hepatotoxic medicinal products or substances

Experience with use of fidanacogene elaparvovec in patients receiving hepatotoxic medicinal product or using hepatotoxic substances is limited. Care should be exercised when administering potential hepatotoxic medicinal substances, herbal supplements, and alcohol to patients treated with fidanacogene elaparvovec, as the efficacy of fidanacogene elaparvovec may be reduced, and the risk of serious hepatic reactions may increase following fidanacogene elaparvovec administration.

Prior to fidanacogene elaparvovec administration, the patient's existing concomitant medicinal products should be reviewed to determine if they should be modified to prevent possible anticipated interactions. After fidanacogene elaparvovec administration, patients' concomitant medications should be monitored particularly during the first year, and the need to change concomitant medicinal products based on patients' 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.

Interactions with medicinal products that may reduce or increase plasma concentrations of corticosteroids

Medicinal products that may reduce or increase the plasma concentration of corticosteroids (e.g., medicinal products 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 fidanacogene elaparvovec infusion, the patient's vaccinations should be confirmed to be up to date. The patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy. 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). Moreover, no data are available to recommend a specific duration of contraceptive measures in women of childbearing potential. Therefore, BEQVEZ is not recommended in women of childbearing potential.

Contraception after administration to males

For 6 months after administration of fidanacogene elaparvovec, treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception and avoid contact with semen. Males treated with fidanacogene elaparvovec 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. Fidanacogene elaparvovec is not recommended during pregnancy.

Breast-feeding

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

Fertility

No information is available on the effects of fidanacogene elaparvovec on female or male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Infusion of fidanacogene elaparvovec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as headaches and dizziness that have occurred shortly after fidanacogene elaparvovec 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 reaction following administration was transaminases increased (43.3%).

Tabulated list of adverse reactions

The safety of fidanacogene elaparvovec was evaluated in 60 patients who received the recommended dose (5×10^{11} vector genomes/kg) in 2 open-label clinical studies. The adverse reactions identified with fidanacogene elaparvovec are presented in Table 5.

Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5. Tabulated list of adverse reactions to fidanacogene elaparvovec

MedDRA system organ class	Adverse reaction	Frequency
Nervous system disorders	Headache, Dizziness	Common
Gastrointestinal disorders	Abdominal pain**, Nausea	Common
Hepatobiliary disorders	Transaminases increased*	Very common
General disorders and administration	Pyrexia, Asthenia	Common
Investigations	Blood creatinine increased, Blood lactate dehydrogenase increased	Common

* Includes terms alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, hepatic enzyme increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
** Includes abdominal pain and epigastric pain.

Description of selected adverse reactions

Hepatic laboratory abnormalities
Forty-three of the 60 (71.7%) patients had ALT elevations and 44 of the 60 (73.3%) patients had AST elevations. Thirty-seven of the 60 (61.7%) patients with ALT elevations also experienced AST elevations. The median onset time of first ALT elevation was 39 days (range: 2 to 2186 days) and the median time to resolution of the first ALT elevation was 13 days (range: 4 to 1373 days). All ALT elevation episodes (52/52) from all participants (36/36) that started within 120 days of fidanacogene elaparvovec infusion resolved. Thirty-one participants had 58 ALT elevation episodes post day 120, and 83% of the episodes had resolved at the time of data cut. Of those unresolved only 3 patients remained > ULN.

Thirty-one out of 60 (51.7%) patients received corticosteroids. The mean time to corticosteroid initiation was 46 days. The mean duration of corticosteroid treatment was 112 days (range: 41 to 276 days). Among those who received corticosteroids (n=31), no patients experienced Grade 3 or above ALT or bilirubin elevations as shown in Table 6 below.

Table 6. Number (%) of patients with ALT or bilirubin elevation and shift in elevation grade between before corticosteroid initiation and post-cessation of corticosteroid treatment

	N=31* n (%)		
≥ Grade 3 ALT elevation prior to corticosteroid treatment^	0 (0%)		
≥ Grade 3 ALT elevation post-cessation of corticosteroid treatment&	0 (0%)		
≥ Grade 3 bilirubin elevation prior to corticosteroid treatment^	0 (0%)		
≥ Grade 3 bilirubin elevation post-cessation of corticosteroid treatment&	0 (0%)		
	Post-cessation of corticosteroid treatment&		
Prior to corticosteroid treatment	**Normal**	**Grade 1**	**Grade 2**
ALT elevation			
Normal	16 (51.6%)	4 (12.9%)	0
Grade 1	8 (25.8%)	2 (6.5%)	0
Grade 2	1 (3.2%)	0	0
Bilirubin elevation			
Normal	28 (90.3%)	3 (9.7%)	0
Grade 1	0	0	0

* Participants who received corticosteroids.
^ The last ALT and bilirubin ALT liver enzyme results prior to the initiation of corticosteroid treatment.
& The peak ALT and bilirubin ALT liver enzyme results post-cessation of corticosteroid treatment.
CTCAE grades for ALT elevation: Grade 1: > ULN to 3.0 × ULN if baseline was normal; 1.5 to 3.0 × baseline if baseline was abnormal. Grade 2: > 3.0 to 5.0 × ULN if baseline was normal; > 3.0 to 5.0 × baseline if baseline was abnormal. Grade 3: > 5.0 to 20.0 × ULN if baseline was normal; > 5.0 to 20.0 × baseline if baseline was abnormal. Grade 4: > 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal.
CTCAE grades for bilirubin elevation: Grade 1: > ULN to 1.5 × ULN if baseline was normal; 1.0 to 1.5 × baseline if baseline was abnormal; Grade 2: > 1.5 to 3.0 × ULN if baseline was normal; > 1.5 to 3.0 × baseline if baseline was abnormal; Grade 3: > 3.0 to 10.0 × ULN if baseline was normal; > 3.0 to 10.0 × baseline if baseline was abnormal; Grade 4: > 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal.

Immunogenicity

The administration of fidanacogene elaparvovec has the potential to generate immunity in the form of neutralising antibodies against the vector capsid, the transgene (viral-derived factor IX) and as a cellular response against the transduced cells producing factor IX.

No patients developed factor IX inhibitors during the clinical studies using fidanacogene elaparvovec. There are currently no data regarding the efficacy of fidanacogene elaparvovec when used in patients with history of factor IX inhibitors.

A sustained increase in neutralising anti-AAVRh74var antibodies has been observed after administration of fidanacogene elaparvovec in all subjects who participated in clinical studies and had neutralising antibody assessment. In the Phase 3 clinical study, the mean neutralising anti-AAVRh74var antibodies titre value at week 52 was 28 531.10 and remained generally elevated at week 156 assessment.

Fidanacogene elaparvovec-treated patients were tested for cellular immune responses to overall capsid pool and overall factor IX pool using an IFN-γ ELISpot assay. ELISpot results did not show a trend of presumed T-cell response (based on positive ELISpot) as a function of time during the 1-year post-infusion period in either the Phase 3 or Phase 1/2 clinical studies.

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 national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of fidanacogene elaparvovec. Close clinical observation and monitoring of laboratory parameters (including clinical chemistry and haematology) for systemic immune response are recommended (see section 4.4). Symptomatic and supportive treatment, as deemed necessary by the treating physician, is advised in the case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood coagulation factors, ATC code: not yet assigned

Mechanism of action

Fidanacogene elaparvovec is a gene therapy designed to introduce a functional copy of the high activity Padua variant of the factor IX gene (FIX-R338L) in the transduced cells to address the monogenic root cause of haemophilia B.

Fidanacogene elaparvovec is a non-replicating recombinant AAV vector that utilises AAVRh74var capsid to deliver a stable human factor IX transgene. AAVRh74var capsid is able to transduce hepatocytes, the natural site of factor IX synthesis. The factor IX gene present in fidanacogene elaparvovec is designed to reside predominately as episomal DNA within transduced cells and expression of the transgene is driven by a liver specific promoter, which results in tissue specific, continuous and sustained factor IX protein expression.

Fidanacogene elaparvovec therapy results in measurable vector-derived coagulation factor IX activity.

Clinical efficacy and safety

The efficacy of fidanacogene elaparvovec was evaluated in an open-label, multi-site Phase 3 study (C0371002, N=45). The study enrolled adult male patients aged 18 - 62 years with moderately severe to severe haemophilia B (factor IX activity ≤ 2%) that were negative for neutralising antibody (nAb) to AAVRh74var and who received a single intravenous infusion dose of fidanacogene elaparvovec at 5×10^{11} vg/kg of body weight. The patients will continue follow-up post-infusion for a total of 6 years per patient. All patients completed a lead-in study of at least 6 months to capture baseline bleed and infusion data, where the patients were receiving prophylaxis as usual care. These data served as the control for comparison with post-fidanacogene elaparvovec infusion efficacy data.

The study excluded patients with active hepatitis B or C infection, ALT/AST/ALP > 2 × ULN, bilirubin > 1.5 × ULN, unstable liver or biliary disease, and significant liver fibrosis. Thirty-three of 45 (73.3%) patients were White, 7 (15.6%) were Asian, 1 (2.2%) was Black or African American and 4 (8.9%) were not reported.

The primary efficacy endpoint was annualised bleeding rate (ABR) for total bleeds (treated and untreated) from week 12 to month 15 versus usual care factor IX prophylaxis replacement regimen, comparing pre- and post-fidanacogene elaparvovec infusion.

The secondary endpoints included ABR for treated bleeds, annualised infusion rate (AIR) of exogenous factor IX, and annualised FIX consumption, all from week 12 to month 15. Vector-derived factor IX activity level is presented up to 36 months.

ABR and annualised use of exogenous factor IX

ABR_{total} collected in the lead-in period prior to vector infusion while receiving routine care prophylaxis regimen was 4.50 (95% CI: 1.84, 7.16) and ABR_{total} from week 12 to month 15 post-fidanacogene elaparvovec infusion was 1.44 (95% CI: 0.57, 2.31). Fidanacogene elaparvovec resulted in statistically significant decrease of ABR_{total} (treatment difference and 95% CI: -3.06 [-5.34, -0.78], two-sided p = 0.0084) compared with factor IX prophylaxis.

Six out of 45 (13.3%) patients have resumed factor IX prophylaxis post-fidanacogene elaparvovec infusion (primary reason: 5 due to low FIX:C and 1 due to bleed frequency), with time to resumption ranging from 5.1 months to 20.5 months.

The efficacy results of fidanacogene elaparvovec with respect to ABR_{total}, ABR_{treat}, ABR_{total} of specific types (spontaneous, joint, target joint), AIR and annualised FIX consumption are shown in Table 7.

Table 7. C0371002 study: annualised bleed rate, annualised factor infusions and annualised factor IX consumption

	Factor IX prophylaxis (N=45)	**BEQVEZ (N=45)**
ABR_{total}*		
Model based estimate (95% CI)	4.50 (1.84, 7.16)	1.44 (0.57, 2.31)
Treatment difference (95% CI)		−3.06 (−5.34, −0.78)
p-value for treatment difference		0.0084
Percent reduction (95% CI)		68.0% (44.3%, 81.7%)
n (%) of patients without any bleeds	13 (28.9)	28 (62.2)
ABR_{treat}		
Model based estimate (95% CI)	3.34 (1.70, 4.98)	0.73 (0.23, 1.23)
Treatment difference (95% CI)		-2.61 (-4.27, -0.96)
p-value for treatment difference		0.0020
Percent reduction (95% CI)		78.2% (51.6%, 90.1%)
n (%) of patients without any bleeds	16 (35.6)	33 (73.3)
ABR_{total} of spontaneous bleeding		
Model based estimate (95% CI)	3.23 (0.91, 5.56)	0.68 (0.19, 1.18)
p-value for treatment difference		0.0191
Percent reduction (95% CI)		78.9% (56.0%, 89.9%)
n (%) of patients without any bleeds	18 (40.0)	35 (77.8)
ABR_{total} of joint bleeding		
Model based estimate (95% CI)	3.73 (1.32, 6.14)	0.85 (0.33, 1.38)
p-value for treatment difference		0.0100
Percent reduction (95% CI)		77.2% (57.4%, 87.8%)
n (%) of patients without any bleeds	20 (44.4)	31 (68.9)
ABR_{total} of target joint bleeding		
Model based estimate (95% CI)	2.54 (0.28, 4.80)	0.39 (0.02, 0.75)
p-value for treatment difference		0.0372
Percent reduction (95% CI)		84.8% (68.8%, 92.6%)
n (%) of patients without any bleeds	37 (82.2)	39 (86.7)

	Factor IX prophylaxis (N=45)	BEQVEZ (N=45)
AIR		
Mean (SD)	58.83 (29.056)	4.54 (10.026)
Median (Q1, Q3)	52.58 (46.81, 71.22)	0.00 (0.00, 3.77)
Percent reduction		92.3%
n (%) of patients without any infusions	0	29 (64.4)
Annualised factor IX consumption (IU/kg)		
Mean (SD)	3 168.56 (1 635.545)	239.39 (539.617)
Median (Q1, Q3)	2 350.07 (2 010.78, 4 353.49)	0.00 (0.00, 177.09)
Percent reduction		92.4%

* Bleeding events that occurred post-resumption of prophylaxis were included in the analysis from week 12 to month 15.

Analysis period was from week 12 to month 15 post-infusion of BEQVEZ. No participant withdrew from the study prior to month 15.

Model based ABR estimates and two-sided p-value for treatment difference from a repeated measures generalised linear model (GLM) with negative binomial distribution and identity link function.

Percent reduction for ABR from a repeated measures GLM with negative binomial distribution and log link function.

ABR_{total} = Annualised Bleed Rate for all bleeds (treated and untreated with factor IX, excluding procedural bleeds).

ABR_{treat} = Annualised Bleed Rate for treated bleeds (treated with factor IX, excluding procedural bleeds).CI = confidence interval.

AIR = Annualised Infusion Rate (for any reason, including perioperative infusions).

Factor IX activity

From week 12 onward, the levels of factor IX remained stable. Factor IX activity level over time by assay is presented in Table 8.

Table 8. C0371002 study: factor IX activity over time by assay

				Change from baseline[$]		
Visit	**n**	**Mean (SD)**	**Median (min, max)**	**LS mean (SE)[^]**	**95% CI[^]**	**One-sided p-value[^]**
One-stage assay (SynthASil reagent)[*]						
Week 12	44	27.79 (15.226)	26.45 (3.2, 68.6)	26.63 (2.671)	(21.39, 31.87)	< 0.0001
Month 6	39	27.64 (21.373)	23.20 (0.9, 99.7)	26.25 (2.679)	(21.00, 31.51)	< 0.0001
Month 15	39	26.17 (25.100)	22.50 (0.9, 119.0)	24.70 (2.678)	(19.44, 29.95)	< 0.0001
Month 24	39	26.47 (25.092)	22.90 (0.9, 123.4)	24.66 (2.688)	(19.38, 29.93)	< 0.0001
Month 36	13	23.83 (19.165)	21.80 (0.9, 74.8)	25.47 (3.021)	(19.54, 31.40)	< 0.0001
One-stage assay (Actin FSL reagent)						
Week 12	44	13.58 (8.047)	13.58 (1.7, 35.1)	12.53 (1.806)	(8.99, 16.08)	< 0.0001
Month 6	41	13.08 (11.170)	10.10 (0.6, 55.0)	11.93 (1.808)	(8.38, 15.47)	< 0.0001
Month 15	39	13.96 (15.403)	10.20 (0.9, 69.8)	12.57 (1.810)	(9.02, 16.12)	< 0.0001
Month 24	38	15.70 (16.392)	12.85 (0.9, 87.3)	13.81 (1.818)	(10.24, 17.37)	< 0.0001
Month 36	13	14.57	12.50	16.88	(12.86, 20.90)	<0.0001

				Change from baseline[$]		
Visit	**n**	**Mean (SD)**	**Median (min, max)**	**LS mean (SE)[^]**	**95% CI[^]**	**One-sided p-value[^]**
		(12.473)	(0.9, 47.6)	(2.049)		
Chromogenic assay						
Week 12	44	13.91 (9.302)	12.05 (1.4, 36.3)	12.78 (1.561)	(9.71, 15.84)	< 0.0001
Month 6	40	14.81 (12.988)	10.30 (0.9, 57.7)	13.04 (1.569)	(9.96, 16.12)	< 0.0001
Month 15	38	15.19 (16.647)	10.00 (0.9, 74.2)	13.60 (1.571)	(10.52, 16.69)	< 0.0001
Month 24	39	14.61 (16.648)	9.60 (0.9, 80.3)	13.07 (1.582)	(9.96, 16.17)	< 0.0001
Month 36	13	11.62 (10.549)	10.10 (0.9, 40.8)	10.45 (1.958)	(6.61, 14.29)	< 0.0001

Any samples taken within 7 days (14 days if extended half-life product was used) of exogeneous FIX replacement therapy were not eligible.
If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the assessments at the visits following withdrawal/dropout/resumption were imputed as 1.9% based on their baseline disease severity (0.9% if severe and 1.9% if moderately severe).

* Silica-based one-stage assay
[$] Baseline FIX:C was imputed based on the reported baseline disease severity level. If the participant was in severe category (FIX:C < 1%), the baseline FIX:C was imputed as 0.9%. If the participant was in the moderately severe category (FIX:C 1 to ≤ 2%), the baseline FIX:C was imputed as 1.9%.
[^] Least square (LS) mean, standard error (SE), 95% CI, and one-sided p-value were from repeated measures linear mixed effect model (MMRM) with participant as the random effect, and study visit as a fixed effect. Study visits with n ≥ 10 were included in the model.

The proportions of Study C0371002 participants achieving specific factor IX activity level thresholds over time by assay are presented in Table 9.

At month 15, 85% (33 out of 39) patients were in or above mild range (FIX activity ≥ 5%) based on one-stage SynthASil assay, and 67% and 71% based on one-stage Actin FSL assay and chromogenic assay, respectively. At month 24, 82% (32 out of 39) patients were in or above mild range (FIX activity ≥ 5%) based on one-stage SynthASil assay, and 71% and 69% based on one-stage Actin FSL assay and chromogenic assay, respectively.

Table 9. Participants achieving factor IX activity category in study C0371002 over time

		BEQVEZ (N=45)		
Visit	**FIX:C category**	**One-stage assay (SynthASil reagent)* n (%)**	**One-stage assay (Actin FSL reagent) n (%)**	**Chromogenic assay n (%)**
Week 12	**Total**	**44**	**44**	**44**
	0 - < 5%	1 (2.3)	8 (18.2)	9 (20.5)
	5 - < 15%	8 (18.2)	19 (43.2)	19 (43.2)
	15 - < 40%	25 (56.8)	17 (38.6)	16 (36.4)
	40 - < 150%	10 (22.7)	0	0
	≥150%	0	0	0

		BEQVEZ (N=45)		
Visit	**FIX:C category**	**One-stage assay (SynthASil reagent)* n (%)**	**One-stage assay (Actin FSL reagent) n (%)**	**Chromogenic assay n (%)**
Month 6	**Total**	**39**	**41**	**40**
	0 - < 5%	4 (10.3)	9 (22.0)	8 (20.0)
	5 - < 15%	4 (10.3)	22 (53.7)	19 (47.5)
	15 - < 40%	25 (64.1)	8 (19.5)	10 (25.0)
	40 - < 150%	6 (15.4)	2 (4.9)	3 (7.5)
	≥ 150%	0	0	0
Month 15	**Total**	**39**	**39**	**38**
	0 - < 5%	6 (15.4)	13 (33.3)	11 (28.9)
	5 - < 15%	9 (23.1)	12 (30.8)	14 (36.8)
	15 - < 40%	15 (38.5)	12 (30.8)	10 (26.3)
	40 - < 150%	9 (23.1)	2 (5.1)	3 (7.9)
	≥ 150%	0	0	0
Month 24	**Total**	**39**	**38**	**39**
	0 - < 5%	7 (17.9)	11 (28.9)	12 (30.8)
	5 - < 15%	7 (17.9)	12 (31.6)	14 (35.9)
	15 - < 40%	18 (46.2)	13 (34.2)	10 (25.6)
	40 - < 150%	7 (17.9)	2 (5.3)	3 (7.7)
	≥ 150%	0	0	0
Month 36	**Total**	**13**	**13**	**13**
	0 - < 5%	2 (15.4)	2 (15.4)	4 (30.8)
	5 - < 15%	3 (23.1)	6 (46.2)	6 (46.2)
	15 - < 40%	7 (53.8)	4 (30.8)	2 (15.4)
	40 - < 150%	1 (7.7)	1 (7.7)	1 (7.7)
	≥ 150%	0	0	0

Any samples taken within 7 days (14 days if extended half-life product is used) of exogeneous FIX replacement therapy were not eligible.
If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the assessments at the visits following withdrawal/dropout/resumption were imputed based on their baseline disease severity (0.9% if severe and 1.9% if moderately severe).
* Silica-based one-stage assay

Long-term effect
In Study C0371002, efficacy remained stable during year 2 to year 4 post-fidanacogene elaparvovec infusion (Table 10).

Table 10. Summary of ABR_{total}, AIR, and annualised factor IX consumption over time*

	Year 2 (month 15 to month 24) (N=44)	**Year 3 (month 24 to month 36) (N=40)**	**Year 4 (month 36 to month 48) (N=15)**	**Overall follow-up# (N=45)**
ABR_{total}				
Number (%) of patients without any bleeds	33 (84.6)	27 (79.4)	13 (86.7)	27 (60.0)
Mean (SD)	0.39 (1.110)	0.61 (1.624)	0.29 (0.776)	1.09 (2.208)
Median (min, max)	0.00 (0.0, 5.6)	0.00 (0.0, 8.2)	0.00 (0.0, 2.6)	0.00 (0.0, 9.9)

	Year 2 (month 15 to month 24) (N=44)	Year 3 (month 24 to month 36) (N=40)	Year 4 (month 36 to month 48) (N=15)	Overall follow-up[#] (N=45)
AIR				
Number (%) of patients without any infusions	33 (75.0)	29 (72.5)	12 (80.0)	25 (55.6)
Mean (SD)	6.52 (18.697)	4.90 (14.871)	1.40 (4.691)	4.84 (11.085)
Median (min, max)	0.00 (0.0, 92.4)	0.00 (0.0, 81.2)	0.00 (0.0, 18.3)	0.00 (0.0, 53.3)
Annualised FIX consumption (IU/kg)				
Mean (SD)	301.34 (852.206)	219.01 (570.946)	56.28 (186.122)	230.51 (498.669)
Median (min, max)	0.00 (0.0, 4402.7)	0.00 (0.0, 2752.5)	0.00 (0.0, 724.7)	0.00 (0.0, 2304.8)
Number of participants resumed FIX prophylaxis (n)	1	0	0	6[$]

* Patients had varying length of follow-up post-infusion of fidanacogene elaparvovec, and bleeding and infusion rates were annualised within each time period.

[#] From Week 12 to 30 Aug 2023

[$] Five (5) participants resumed FIX prophylaxis between month 5 and month 15.

If prophylaxis FIX regimen was resumed for a patient, then the time period following the resumption of the prophylaxis regimen was excluded from ABR endpoint calculation, but still included in the AIR calculation.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with BEQVEZ in one or more subsets of the paediatric population in the treatment of congenital factor IX deficiency (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

Fidanacogene elaparvovec vector DNA levels were measured and quantified in blood and various shedding matrices using a quantitative polymerase chain reaction (qPCR) assay. This assay is sensitive and specific to fidanacogene elaparvovec vector DNA, but could also detect DNA fragments.

Clinical pharmacokinetics and shedding

Vector shedding after infusion with fidanacogene elaparvovec was assessed in 60 patients at multiple time points in clinical studies (C0371005/C0371003 and C0371002). Vector DNA was shed in peripheral blood mononuclear cells (PBMC), saliva, urine, semen, and serum/plasma. In general, peak levels of vector DNA occurred within the first two weeks after infusion. Highest peak vector DNA concentrations were found in serum/plasma compared to the other liquid matrices (saliva, urine, semen). In plasma (measured only in C0371002), mean peak vector DNA concentration of 2.008×10^9 vg/mL was observed. The mean peak vector DNA concentration in any shedding matrix was 6.261×10^6 vg/mL.

Full clearance of vector DNA was defined as having 3 consecutive negative results (i.e., below quantification limit; BQL). Vector DNA fully cleared in serum, plasma, saliva, and semen within a

mean of 1-4 months after infusion and PBMC was slowest fluid to full clearance within a mean of 12 months. In urine, the peak vector DNA concentration was very low relative to plasma and declined to full clearance within a mean of 4 weeks after infusion. Across studies, the maximum observed time for vector DNA full clearance in saliva, urine and semen were 105 days, 87 days and 154 days, respectively.

To further characterise the shed material, saliva, semen, and urine samples from a subset of 17 patients in Study C0371002 were tested using nuclease treatment (MNase) prior to DNA extraction. Nuclease treatment digests the free floating vector DNA so it cannot be quantified, ensuring the material being quantified following digestion is only encapsulated viral DNA. After nuclease treatment and subsequent DNA extraction, the amount of fidanacogene elaparvovec was measured by qPCR. In saliva, mean concentrations were similar up to week 2 between the MNase treatment and without MNase treatment subgroups, while all participants had concentrations BQL by week 9. In semen, mean concentrations were approximately 33% lower in the MNase treatment subgroup until week 3, and BQL for all participants by week 11. In urine, mean concentrations were approximately 30% lower in the MNase treatment subgroup until 72 h post-infusion and were BQL for all participants by week 2.

5.3 Preclinical safety data

General toxicity

No adverse findings were observed in a 90-day single-dose intravenous general toxicity study in cynomolgus monkeys at doses up to 5×10^{12} vg/kg (10 times the recommended human dose). In a monkey biodistribution study, 22 tissues were collected 30 and 92 days following treatment. The highest levels of vector DNA were found in liver with levels approximately 20-fold higher than spleen, the organ with second most abundant levels of genomic DNA. There was very little biodistribution to testes.

Genotoxicity

In a 2-year vector integration study in cynomolgus monkeys administered 5×10^{12} vg/kg (10 times the recommended human dose), there was no indication that integration of vector DNA into host cell DNA resulted in altered liver function, or hepatocellular hyperplasia and carcinoma up to 2 years. The integration profile was considered benign as the integrations were generally random with a low frequency that was below published spontaneous mutation rate estimates for the liver and due to the absence of significant clonal expansion. Nonclinical safety data available beyond 2 years has not been established.

Carcinogenicity

Carcinogenicity studies have not been conducted. The results of the integration site analysis conducted in cynomolgus monkeys and haemophilia B dogs indicated a benign profile and there was no evidence of clonal expansion. There was no evidence of hepatocellular hyperplasia in monkeys at the 92-day or 2-year necropsied, nor in mice in the 1-year study.

Reproductive and developmental toxicity

No dedicated reproductive and developmental toxicity studies, including embryofoetal and fertility assessments, were performed with fidanacogene elaparvovec, as males comprise the majority of the patient population to be treated with fidanacogene elaparvovec. The potential for germline transmission has been evaluated in male rabbits and vector was no longer detectable in semen at 5 months post-administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate (E339)
Disodium hydrogen phosphate heptahydrate (E339)
Sodium chloride
Poloxamer 188
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened frozen vials

3 years

Unopened thawed vials

Frozen vials in the inner carton will take up to 1-hour to thaw at room temperature (up to 30 °C). The total time at room temperature between removing vials from frozen storage until the beginning of dose preparation should be no more than 3 hours.

Once thawed, the medicinal product should not be re-frozen and may be stored refrigerated at 2 °C to 8 °C in the inner carton for 24 hours.

Diluted solution for infusion

Following dilution in sodium chloride 9 mg/mL (0.9%) solution for injection with 0.25% human serum albumin (HSA), chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 30 °C. The administration of fidanacogene elaparvovec dose to the patient should be completed within 24 hours after dose preparation.

6.4 Special precautions for storage

Store at −90 °C to −60 °C and transport at −100 °C to −60 °C. Original packages removed from frozen storage (−90 °C to −60 °C) may be kept at room temperature (up to 30 °C) for up to 5 minutes for transfer between ultra-low temperature environments.

Store upright in the original package in order to protect from light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

BEQVEZ is supplied in a 2 mL cyclic olefin copolymer vial with an elastomeric stopper and plastic snapfit cap. Each vial contains sufficient volume to ensure 1 mL of extractable volume.

The total number of vials in each finished pack corresponds to the dosing requirement of the individual patient, depending on the body weight and actual concentration, and is provided on the package and LIS. The finished pack will consist of vials, which are included in the inner carton, and placed in the outer carton (patient-specific pack).

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

BEQVEZ should be transported within the facility in closed, break-proof, and leak-proof containers.

This medicinal product contains genetically modified organisms.

BEQVEZ should be handled aseptically under sterile conditions.

Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering BEQVEZ.

Thawing

- Store in the original package to avoid direct sunlight and ultraviolet light exposure.
- Store BEQVEZ upright in the original package.
- Remove inner carton from the outer carton.
- Thaw BEQVEZ vials in the upright orientation in the inner carton for 1-hour at room temperature (15 °C to 30 °C).
- Vials may be gently swirled but not shaken or inverted.
- The total time at room temperature between removing vials from frozen storage until the beginning of dose preparation should be no more than 3 hours.
- Visually inspect vials for particulates and discolouration before use. Ensure that visible ice crystals are not present in the solution. Do not use vials that contain visible particulates. The thawed solution in the vial should appear clear to slightly opalescent, colourless to slightly brown solution.
- Vials should not be re-frozen.

Preparation prior to administration

This medicinal product is prepared for intravenous infusion by diluting in sodium chloride 9 mg/mL (0.9%) solution for injection with 0.25% human serum albumin (HSA).

Preparation of diluent solution (sodium chloride 9 mg/mL (0.9%) solution for injection with 0.25% HSA)

- HSA used for preparation of this medicinal product must be commercially available. Either 20% w/v or 25% w/v HSA is recommended.
- Calculate the volume of HSA required to achieve a final concentration of 0.25% w/v HSA in a 200 mL final infusion volume.
- Calculate the volume of medicinal product required for the patient-specific treatment.
    - See the accompanying LIS for information pertaining to the concentration of vector genomes per vial, and for the medicinal product calculation steps.

- Note: The vector genomes concentration on the LIS is the actual concentration of each vial which should be used for dose preparation calculations.

- Calculate the volume of sodium chloride 9 mg/mL (0.9%) solution for injection required to achieve a final infusion volume of 200 mL when combined with the medicinal product and HSA.

- Combine the calculated volume of HSA with the calculated volume of sodium chloride 9 mg/mL (0.9%) solution for injection in an appropriate intravenous infusion container.

- Mix the diluent solution gently. Do not shake. Incubate the diluent solution in the infusion container at room temperature (15 °C to 30 °C) for at least 10 minutes prior to adding BEQVEZ.

Preparation of solution for infusion

- Visually inspect thawed product for particulate matter prior to administration. Do not use vials that contain visible particulates.

- Each vial is for single use only.

- Extract the calculated volume of BEQVEZ from the vials using aseptic technique and sterile componentry.

- Combine the extracted volume of BEQVEZ with the diluent solution (0.9% sodium chloride with 0.25% HSA) for a total infusion volume of 200 mL.

- Gently mix the solution for infusion. Do not shake.

- The solution for infusion should be equilibrated to ambient temperature before administration to the patient.

Administration of solution for infusion

- For intravenous use.

- Do not infuse as an intravenous push or bolus.

- An in-line 0.2 µm intravenous filter may be used for administration.

- The solution for infusion should be administered to the patient over approximately 60 minutes.

- In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped (see section 4.4).

Measures to take in case of accidental exposure

Accidental exposure to BEQVEZ must be avoided. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water according to local procedures. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable materials that may have come in contact with BEQVEZ (e.g., vials, all materials used for injection, including needles and any unused product) must be disposed of in compliance with the local guidance for pharmaceutical waste.

All spills of BEQVEZ must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of per local guidelines for handling of pharmaceutical waste.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1838/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 July 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) 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

Wyeth Holdings LLC
4300 Oak Park Road
Sanford NC 27330-9550
USA

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

Wyeth Farma S.A.
Autovia del Norte A-1 Km. 23. Desvio Algete Km. 1
28700 San Sebastian de los Reyes
Madrid
Spain

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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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 the launch of BEQVEZ in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at providing information on the safe use of BEQVEZ and to inform about important risks associated with BEQVEZ.

The MAH shall ensure that in each Member State where BEQVEZ is marketed, all healthcare professionals and patients/carers who are expected to prescribe, use or oversee the administration of BEQVEZ have access to/are provided with the following educational package. These documents 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:

- The Summary of Product Characteristics
- The Guide for Healthcare Professionals
- The Patient Guide
- The Patient Card

The Guide for Healthcare Professionals:

- Patients should be selected for treatment with BEQVEZ based on the absence of pre-existing antibodies to AAVRh74var using a validated assay and status of liver health based on laboratory and imaging data.
- To inform of the important identified risks of hepatotoxicity and the important potential risks of development of factor IX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission) and germline transmission, and missing information of long-term safety 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 BEQVEZ with the patient when presenting BEQVEZ as a treatment option, including:
    - That no predictive factors for no or low responders have been identified. Patients who do not respond are still exposed to long-term risks.
    - That the long-term treatment effects 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.

- Reminding patients about the importance to enrol in a registry for follow-up of long-term effects.

- That BEQVEZ use will require in some cases co-administration of corticosteroids to manage the liver damage that this medicinal product might induce. This requires adequate monitoring of patients and careful consideration of other co-medications, herbal supplements, and/or alcohol to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of BEQVEZ.

- That the patient should be routinely tested for factor IX inhibitors development after BEQVEZ treatment.

- That the patient will be provided the patient guide and the patient card by the healthcare professional.

The Patient Information Pack consists of

- The Patient Information Leaflet
- The Patient Guide
- The Patient Card

The Patient Guide:

- Importance of fully understanding the benefits and risks of BEQVEZ treatment, what is known and not yet known about the long-term effects, related to safety and efficacy.
- Therefore, before a decision is made about starting on the therapy the doctor will discuss with the patient the following:
    - That BEQVEZ will, in some cases, require co-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 responses to BEQVEZ 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 not all patients may benefit from treatment with BEQVEZ and the reasons for this have not been established. Patients not responding to treatment will still be exposed to long-term risks of BEQVEZ.
    - Details how the important potential risks of development of factor IX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission) and germline transmission can be recognised and minimised by regular monitoring as recommended by doctors.
        - The patient should seek immediate medical advice for any symptoms suggestive of a thromboembolic event.
        - Male patients or their female partners should use barrier contraception for six months after administration of BEQVEZ.
        - That BEQVEZ 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 BEQVEZ treatment is needed in patients with pre-existing risk factors for hepatocellular carcinoma.

- Patients must not donate blood, semen, or organs, tissues, and cells for transplantation.

- That the Patient Card should be carried by the patient at any time and shared with any doctor or 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:

- This card is to inform healthcare professionals that the patient has received BEQVEZ 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.
- That 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 BEQVEZ.
- The patient must not donate blood, semen, organs, tissues and cells for transplantation.
- Male patients should ensure that they use a barrier method of contraception for 6 months after receiving BEQVEZ.
- **Obligations to conduct post-authorisation measures**

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

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy and safety of BEQVEZ in adults with severe and moderately severe haemophilia B (congenital factor IX deficiency) without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74, the MAH should conduct and submit the final results of registry-based Study C0371007, according to an agreed protocol.	31 December 2045
Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy and safety of BEQVEZ in adults with severe and moderately severe haemophilia B, the MAH should submit the final results of Study C0371017, which includes patients who have been treated with BEQVEZ in all MAH-sponsored clinical trials.	31 March 2040

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 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 BEQVEZ in adults with severe and moderately severe haemophilia B (congenital factor IX deficiency) without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74, the MAH should submit interim results (6 years of data) of pivotal Study C0371002 with 45 subjects who received a dose calculated using actual batch concentration and at least 34-month data of patients who received a dose based on nominal concentration dosing.	31 December 2028
In order to confirm the efficacy and safety of BEQVEZ in adults with severe and moderately severe haemophilia B (congenital factor IX deficiency) without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74, the MAH should submit the final results (5 years of data) of long-term follow-up Study C0371003 with 14 subjects who received 5×10^{11} vector genomes per kg (vg/kg) of body weight.	31 January 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL concentrate for solution for infusion
fidanacogene elaparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.79 - 1.21 × 10^{13} vector genomes of fidanacogene elaparvovec in 1 mL.

3. LIST OF EXCIPIENTS

Also contains sodium dihydrogen phosphate monohydrate (E339), disodium hydrogen phosphate heptahydrate (E339), sodium chloride, poloxamer 188, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

See actual concentration and Lot Information Sheet for patient dose calculation.

Actual concentration vg/mL

Number of vials vials. Each vial contains 1 mL deliverable volume.

Patient-specific pack containing sufficient amount of vials to dose each patient.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Single use only.

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 at −90 °C to −60 °C and transport at −100 °C to −60 °C.

Store upright in the original package in order to protect from light.

After thawing, do not refreeze. See the package leaflet for additional storage information.

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

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1838/001

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL concentrate for solution for infusion
fidanacogene elaparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.79 - 1.21 × 10^{13} vector genomes of fidanacogene elaparvovec in 1 mL.

3. LIST OF EXCIPIENTS

Also contains sodium dihydrogen phosphate monohydrate (E339), disodium hydrogen phosphate heptahydrate (E339), sodium chloride, poloxamer 188, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

See actual concentration and Lot Information Sheet for patient dose calculation.

Actual concentration vg/mL

Number of vials vials. Each vial contains 1 mL deliverable volume.

Patient-specific pack containing sufficient amount of vials to dose each patient.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Single use only.

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 at −90 °C to −60 °C and transport at −100 °C to −60 °C.

Store upright in the original package in order to protect from light.

After thawing, do not refreeze. See the package leaflet for additional storage information.

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.
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EU/1/24/1838/001

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

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (CONCENTRATE)

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

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL sterile concentrate
fidanacogene elaparvovec
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET (LIS) INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL concentrate for solution for infusion
fidanacogene elaparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.79 - 1.21 × 10^{13} vector genomes of fidanacogene elaparvovec in 1 mL.

The actual concentration noted below should be used to calculate the patient dose.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND DOSE OF THE MEDICINAL PRODUCT

PATIENT DOSE CALCULATION

Each vial contains 1 mL deliverable volume.

The recommended dose of BEQVEZ is a single-dose of 5 × 10^{11} vector genomes per kg (vg/kg) of body weight, administered as an intravenous infusion after dilution

Patient weight (kg): _____ Height (m): _____ BMI (kg/m^2): _____

To determine the patient's dose, the following calculation steps are needed:

1. Calculation of patient's dose weight
The dosing of BEQVEZ is based on the patient body mass index (BMI) in kg/m^2.

Patient's dose weight adjustment according to BMI

Patient's BMI	**Patient's dose weight adjustment**
≤ 30 kg/m^2	Dose Weight = Actual body weight
> 30 kg/m^2	Determine using the following calculation: Dose Weight (kg) = 30 kg/m^2 × [Height (m)]^2

Note:
- The intermediate calculation of height (m^2) should NOT be rounded.
- Dose weight should be rounded to 1 decimal place.

2. Calculation of patient's dose volume in millilitres (mL)
Patient's dose weight in kg × dose per kilogram (5 × 10^{11} vg/kg) = dose in vg to be administered

_____ kg ×5 × 10^{11} vg/kg = _____ vg

Dose in vg to be administered ÷ Actual concentration (vg/mL) = patient's dose volume in mL

_____ vg ÷ _____ (vg/mL) = _____ mL

4. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

5. OTHER SPECIAL WARNING(S), IF NECESSARY

Save this document and have it available when preparing for administration of BEQVEZ.

6. SPECIAL STORAGE CONDITIONS

7. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

INFORMATION ON SUPPLIED LOT

The following lot was manufactured and included in this shipment:

Lot Number
Number of Vials
Actual Concentration (vector genomes/mL)
Expiry Date

8. 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.

9. BATCH NUMBER, DONATION AND PRODUCT CODES

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

11. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1838/001

B. PACKAGE LEAFLET

Package leaflet: Information for the user

BEQVEZ 0.79 - 1.21 × 10^{13} vector genomes/mL concentrate for solution for infusion
fidanacogene elaparvovec

▼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.
- If you get any side effects, talk to your doctor. 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 BEQVEZ is and what it is used for

BEQVEZ is a gene therapy product that contains the active substance fidanacogene elaparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic defect.

BEQVEZ 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 to factor IX and who do not have antibodies to the virus vector AAV serotype Rh74var.

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 BEQVEZ works
The active substance in BEQVEZ, fidanacogene elaparvovec, delivers a working version of the factor IX gene into the body to correct the genetic defect that causes the bleeding problems. The gene is integrated into a virus that has been modified so that it cannot spread in the body but can deliver a copy of the factor IX gene into your liver cells. This enables liver cells to produce factor IX protein and raise the levels of working factor IX in the blood. This helps the blood to clot better and prevents or reduces bleeding episodes.

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

You must not be given BEQVEZ
- if you are allergic to fidanacogene elaparvovec or 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 (see section 2 Warnings and precautions).
- if you have advanced hepatic fibrosis (liver tissue scarring and thickening) or advanced hepatic cirrhosis (scarring due to long-term liver damage) (see section 2 Warnings and precautions).

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 BEQVEZ.

Warnings and precautions

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

Antibody blood tests

Your doctor will conduct a blood test beforehand to see if you have antibodies (proteins) directed against the type of virus used to make this medicine. These antibodies can prevent the medicine from working properly.

Tests to check liver health

Factor IX is produced in liver cells after treatment with BEQVEZ. Talk to your doctor if you have or had any liver problems.

This medicine may lead to an increase in certain enzymes (proteins found in the body) that the liver normally produces when it is damaged.

In order to decide if this medicine is suitable for you, your doctor will perform tests to check your liver health before you start treatment. This includes:
- Blood tests to check your level of liver enzymes and bilirubin (a breakdown product of red blood cells);
- Tests to check for fibrosis (tissue scarring and thickening) in your liver.

Talk to your doctor about what you can do to improve and maintain your liver's health including being aware of how other medicines you may take may affect the liver (see section 2 Other medicines and BEQVEZ).

After treatment with BEQVEZ

Infusion-related side effects

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

Symptoms of infusion-related side effects may include low blood pressure, fever, palpitation, nausea, vomiting, chills or headache. Tell your doctor **immediately** if you experience these or any other symptoms during or shortly after the treatment 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 medicines to help manage the infusion reaction.

Regular blood tests

After treatment with BEQVEZ, 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.

During the first year, your doctor will repeat liver enzyme testing and factor IX testing once or twice weekly for the first 12 weeks, weekly from weeks 13 to 18, and at weeks 24, 32, 42, and 52. Then, from year 2 to end of year 3 testing will be performed quarterly, moving to twice yearly from year 4 to the end of year 6, and annually after year 6.

<u>*Liver enzymes*</u>
BEQVEZ will trigger a response within your immune system (the body's natural defences). This could lead to an increased blood level of certain liver enzymes called transaminases. Your doctor will regularly monitor your liver enzyme levels to ensure that the medicine is working as it should:

- 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.
- If needed, your doctor may also perform additional tests to rule out other causes for an increase in your liver enzymes, in consultation with a specialist in liver diseases.
- <u>Additional medicine:</u> You may need to take another medicine (corticosteroids) for 2 months or longer after starting treatment to manage transaminase increases or a reduction in factor IX activity seen in laboratory tests. Your doctor may adjust the dose of this medicine depending on your blood test results and response.

<u>*Factor IX levels*</u>
Your doctor will regularly check your factor IX levels to see if treatment with BEQVEZ was successful. 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 the other medicine.

Neutralising antibodies against factor IX proteins (factor IX inhibitors)

After you are given BEQVEZ, there is a risk of your body developing neutralising antibodies against factor IX, which may prevent factor IX from working properly. Your doctor may check your blood for these antibodies, if bleeding episodes cannot be controlled.

Risk of malignancy potentially associated with BEQVEZ

Treatment with BEQVEZ will insert new DNA into your liver cells. Although there is no evidence from the clinical studies with BEQVEZ, this DNA can in theory integrate into the liver cell DNA or the DNA of other body cells. This could contribute to a risk of cancer, such as liver cancer (hepatocellular carcinoma). You should therefore discuss this with your physician.

After treatment with BEQVEZ, you will be expected to enrol in a follow-up study to help study the long-term effect 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 BEQVEZ has inserted into the cell DNA.

If you are a patient with pre-existing risk factors for hepatocellular carcinoma (e.g. you have liver fibrosis, or hepatitis B, hepatitis C, or fatty liver (non-alcoholic fatty liver disease)), your doctor will regularly (e.g. each year) monitor your long-term liver health for at least 5 years after you are given BEQVEZ and perform the following tests:

- Annual liver ultrasound and
- Annual blood test to check for increases in alpha-fetoprotein.

Risk of abnormal blood clots

Factor IX is the protein necessary to form stable clots in your blood. After treatment with BEQVEZ, your factor IX protein level should increase. In some patients, it may 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). You may be at risk of abnormal blood clotting if you have pre-existing 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 older than 50 years).

Consult your doctor immediately if you notice 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.

Immunocompromised patients or patients with HIV or other infection

If you are immunocompromised (when your immune system is weakened, resulting in a reduced ability to fight infections), 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 if you will be able to receive BEQVEZ. The use of BEQVEZ is contraindicated in patients with active infections which are either acute (short-term) infections, or chronic (long-term) infections that are not controlled by medicines (see section 2 You must not be given BEQVEZ).

Use of other haemophilia treatments

After BEQVEZ 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. Talk to your doctor immediately in case of recurrent or uncontrolled bleeding episodes.

Receiving gene therapy again in the future

After receiving BEQVEZ, your immune system will produce antibodies to the proteins found on the shell of the adeno-associated virus (AAV) in BEQVEZ. It is not yet known whether or under which conditions therapy with BEQVEZ may be repeated. If your body is exposed to the medicine a second time, it is not known if these antibodies will recognise the virus and keep the medicine from working. It is also not yet known whether or under which conditions subsequent use of another AAV gene therapy may be possible.

Avoiding blood donations and donations for transplantations

The active substance in BEQVEZ may temporarily be excreted through your blood, semen or bodily waste, a process called shedding (see also section 2 Use of contraception).

To ensure that people without haemophilia B are not exposed to BEQVEZ DNA, you must not donate blood, semen, or organs, tissues and cells for transplantation after you have been treated with BEQVEZ.

Children and adolescents
BEQVEZ should not be used in children or adolescents under 18 years of age because it has not yet been studied in this population.

Other medicines and BEQVEZ
Tell your doctor if you are using, have recently used or might use any other medicines and/or herbal supplements as they may affect the proper function of this medicine.

Some medicines, herbal supplements or alcohol affect the liver, which may impact the response to this medicine and may increase the risk of liver damage. You should inform your doctor about new medicines started after treatment as these medicines may affect your liver.

After treatment with BEQVEZ, you may need corticosteroid treatment (see section 2 Warnings and precautions). As corticosteroids can affect the body's immune system, vaccinations may not work properly. It is important that you have received your vaccinations before you are given BEQVEZ. Your doctor may adjust the timing of vaccinations and may recommend that you do not receive certain vaccinations while on corticosteroid treatment. Corticosteroid treatment may also be affected by other medicines. Talk to your doctor if you have any questions.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or plan to become pregnant, ask your doctor for advice prior to being given BEQVEZ.

- BEQVEZ is not recommended in women who are able to become pregnant or who are pregnant. It is not known whether BEQVEZ can be used safely in these patients as the effects on pregnancy and the unborn child are not known.
- BEQVEZ is not recommended during pregnancy. It is not known whether this medicinal product can cause harm to your unborn baby when administered to you during your pregnancy.
- BEQVEZ 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
Male patients should ensure that they use a barrier method of contraception for 6 months after receiving treatment with BEQVEZ and partners must avoid contact with semen during this period. They should also not donate sperm after receiving treatment.

This is to prevent the theoretical risk that the factor IX gene from a father's BEQVEZ treatment is transmitted to a child or the patient's sexual partner with unknown consequences. Discuss with your doctor which methods of contraception are suitable.

Driving and using machines
People given BEQVEZ have experienced side effects, such as temporary headaches and dizziness that may affect the ability to drive or use machines. If you are experiencing such side effects, you should use caution until you are certain that they do not adversely affect your ability to drive or use machines. Talk to your doctor if you have any questions.

BEQVEZ contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.

3. How BEQVEZ is given

Your treatment will be given at a hospital or haemophilia treatment centre by a doctor who is experienced in the treatment of blood clotting disorders.

The doctor will work out the amount of treatment you will receive according to your weight (5×10^{13} vg/kg). Treatment with BEQVEZ consists of a single infusion (drip) into a vein. The infusion will be given over 1 hour. Your infusion may be slowed if you experience symptoms of an infusion reaction (see section 2 Warnings and precautions).

Additional medicine you may need
You doctor may give you another medicine (corticosteroids) to modulate the body's immune response against the virus. Take this medicine according to the doctor's direction. They may also give some factor IX treatment prior to your infusion.

Discontinuation of exogenous factor IX treatment
It may take several weeks before improved bleeding control is achieved after BEQVEZ infusion.

Your doctor will regularly monitor your blood for the factor IX activity levels, i.e., once or twice weekly for the first 12 weeks, and at regular intervals thereafter, and decide if and when you should receive, reduce, or stop your exogenous factor IX therapy (see section 2 Warnings and precautions).

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

If you are given more BEQVEZ than you should
It is unlikely that you will be given too much of this medicine since the dose is administered in the hospital. However, if you are given too much BEQVEZ, your doctor may need to perform blood tests and treat you as needed.

4. Possible side effects

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

Very common: may affect more than 1 in 10 people
- Increased levels of transaminases (liver enzymes) seen in blood tests.

Common: may affect up to 1 in 10 people
- Headache
- Belly (Abdominal) pain
- Dizziness
- Feeling sick (Nausea)
- Fever (Pyrexia)
- Weakness (Asthenia)
- Increased levels of creatinine (a breakdown product of muscle) seen in blood tests
- Increased levels of lactate dehydrogenase (a marker for tissue damage) seen in blood tests

Talk to your doctor or nurse if you develop any other side effects.

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 BEQVEZ

The following information is for healthcare professionals who will prepare and give the medicine.

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. The expiry date refers to the last day of that month.

BEQVEZ must be stored upright and in its original package in order to protect it from light.

Store at -90 °C to -60 °C and transport at -100 °C to -60 °C. Packages removed from frozen storage (-90 °C to -60 °C) may be kept at room temperature (up to 30 °C) for up to 5 minutes for transfer between ultra-low temperature environments.

After thawing, do not refreeze.

Frozen vials in the inner carton will take up to 1 hour to thaw at room temperature (up to 30 °C). The total time at room temperature between removing vials from frozen storage until the beginning of dose preparation should be no more than 3 hours.

Once thawed, the medicinal product should not be re-frozen and may be stored refrigerated at 2 °C to 8 °C in the inner carton for 24 hours. The shelf-life after dilution is 24 hours.

6. Contents of the pack and other information

What BEQVEZ contains
- The active substance is fidanacogene elaparvovec. Each 1 mL vial contains an approximate concentration of 0.79 - 1.21 × 10^{13} vector genomes/mL.
- The other ingredients are sodium dihydrogen phosphate monohydrate (E339), disodium hydrogen phosphate heptahydrate (E339), sodium chloride, poloxamer 188 and water for injections (see section 2 BEQVEZ contains sodium).

This medicine contains genetically modified organisms.

What BEQVEZ looks like and contents of the pack
BEQVEZ is a concentrate for solution for infusion (sterile concentrate).

BEQVEZ is supplied in a plastic 2 mL vial with an extractable volume of 1 mL.

When thawed, BEQVEZ is a clear to slightly opalescent, colourless to slightly brown solution.

BEQVEZ is supplied in a carton containing the number of vials required for a single patient dose.

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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: https://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

BEQVEZ should be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains genetically modified organisms.

BEQVEZ should be handled aseptically under sterile conditions.

Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering BEQVEZ.

Thawing

- Store in the original package to avoid direct sunlight and ultraviolet light exposure.
- Store BEQVEZ upright in the original package.
- Remove inner carton from the outer carton.
- Thaw BEQVEZ vials in the upright orientation in the inner carton for 1-hour at room temperature (15 °C to 30 °C).
- Vials may be gently swirled but not shaken or inverted.
- The total time at room temperature between removing vials from frozen storage until the beginning of dose preparation should be no more than 3 hours.
- Visually inspect vials for particulates and discolouration before use. Ensure that visible ice crystals are not present in the solution. Do not use vials that contain visible particulates. The thawed solution in the vial should appear clear to slightly opalescent, colourless to slightly brown.
- Vials should not be re-frozen.

Preparation prior to administration

This medicinal product is prepared for intravenous infusion by diluting in sodium chloride 9 mg/mL (0.9%) solution for injection with 0.25% human serum albumin (HSA).

Preparation of diluent solution (sodium chloride 9 mg/mL (0.9%) solution for injection with 0.25% HSA)

- HSA used for preparation of this medicinal product must be commercially available. Either 20% w/v or 25% w/v HSA is recommended.
- Calculate the volume of HSA required to achieve a final concentration of 0.25% w/v HSA in a 200 mL final infusion volume.
- Calculate the volume of medicinal product required for the patient-specific treatment.
    - See the accompanying Lot Information Sheet (LIS) for information pertaining to the concentration of vector genomes per vial, and for the medicinal product calculation steps.
    - Note: The vector genomes concentration on the LIS is the actual concentration of each vial which should be used for dose preparation calculations.
- Calculate the volume of sodium chloride 9 mg/mL (0.9%) solution for injection required to achieve a final infusion volume of 200 mL when combined with the medicinal product and HSA.
- Combine the calculated volume of HSA with the calculated volume of sodium chloride 9 mg/mL (0.9%) solution for injection in an appropriate intravenous infusion container.
- Mix the diluent solution gently. Do not shake. Incubate the diluent solution in the infusion container at room temperature (15 °C to 30 °C) for at least 10 minutes prior to adding BEQVEZ.

Preparation of solution for infusion

- Visually inspect thawed product for particulate matter prior to administration. Do not use vials that contain visible particulates.
- Each vial is for single use only.
- Extract the calculated volume of BEQVEZ from the vials using aseptic technique and sterile componentry.
- Combine the extracted volume of BEQVEZ with the diluent solution (0.9% sodium chloride with 0.25% HSA) for a total infusion volume of 200 mL.
- Gently mix the solution for infusion. Do not shake.
- The solution for infusion should be equilibrated to ambient temperature before administration to the patient.

Administration of solution for infusion

- For intravenous use.
- Do not infuse as an intravenous push or bolus.
- An in-line 0.2 µm intravenous filter may be used for administration.
- The solution for infusion should be administered to the patient over approximately 60 minutes.
- In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped (see section 4.4).

Measures to take in case of accidental exposure

Accidental exposure to BEQVEZ must be avoided. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water according to local procedures. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable materials that may have come in contact with BEQVEZ (e.g., vials, all materials used for injection, including needles and any unused product) must be disposed of in compliance with the local guidance for pharmaceutical waste.

All spills of BEQVEZ must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of per local guidelines for handling of pharmaceutical waste.