

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}**BEQVEZ™**

Fidanacogene elaparvovec

Concentrate for solution for infusion, 1×10^{13} vector genomes/mL

Antihemorrhagic

ATC Code: not yet assigned

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17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BEQVEZ (fidanacogene elaparvovec) is an adeno-associated viral (AAV) vector-based gene therapy indicated for the treatment of adults (aged 18 years or older) with moderately severe to severe Hemophilia B (congenital Factor IX deficiency) who are negative for neutralizing antibodies to variant AAV serotype Rh74.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of BEQVEZ in children below 18 years of age have not been studied. No data are available.

1.2 Geriatrics

Geriatrics: The safety and efficacy of BEQVEZ in patients ≥65 years of age have not been established. No data are available.

2 CONTRAINDICATIONS

BEQVEZ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment must be prescribed and administered in clinical centres by a health professional who is experienced in treating Hemophilia B.

Before administration of BEQVEZ:

Patient selection

For patient selection, baseline testing is required. This includes examinations of:

- Preexisting neutralizing AAVRh74var antibodies (see [7 WARNINGS AND PRECAUTIONS](#)). It is recommended that testing be done as close as possible to infusion (e.g., within approximately 8 weeks). If a patient is positive for AAVRh74var neutralizing antibodies they will not be eligible for treatment with BEQVEZ (see [1 INDICATIONS](#) and [14 CLINICAL TRIALS](#)).
- Factor IX inhibitor presence. In case of a positive test for alloantibodies against Factor IX, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive BEQVEZ.
- Liver health, including:
 - Enzyme testing (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin) within 4 weeks prior to BEQVEZ infusion. It is

recommended that the ALT test is repeated at least once prior to BEQVEZ administration to establish patient's ALT baseline.

- Hepatic ultrasound and fibrosis assessment to confirm no significant liver fibrosis, within 3 months prior to BEQVEZ 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, noting that patients with significant/unstable liver disease were excluded from clinical studies with BEQVEZ (see [7 WARNINGS AND PRECAUTIONS](#)).

- In case of serological evidence of HIV-1 or HIV-2: within 8 weeks prior to infusion, confirm CD4⁺ cell count > 200 mm³ and viral load ≤ 20 copies/mL. In patients who do not meet these criteria, consider retesting. Those who do not meet these criteria are not eligible to receive BEQVEZ.

4.2 Recommended Dose and Dosage Adjustment

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

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

1. Calculation of patient's dose weight

The dose of BEQVEZ is limited by the patient's body mass index (BMI) kg/m². Calculate the dosing weight based on the BMI as per the following table:

Patient's BMI	Patient's Dose Weight
≤ 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

2. Calculation of patient's dose volume in millilitres (mL)

BEQVEZ dose (in mL) = Patient's dose weight in kilograms (calculated in step 1) divided by a factor of 20

The division factor 20 is calculated by dividing the concentration of vector genomes per mL of BEQVEZ solution (1×10^{13} vg/mL) by the per kilogram dose (5×10^{11} vg/kg).

Examples of dose volume calculation:

Patient's Weight, Height and BMI	Patient's Dose Weight Calculation Based on BMI	Patient's Dose Weight	Patient's Dose Volume (Dose Weight Divided by 20)
80 kg, 1.84 m 23.6 kg/m ²	No adjustment	80 kg	4 mL
120 kg, 1.84 m 35.4 kg/m ²	$30 \text{ kg/m}^2 \times [1.84 \text{ (m)}]^2$	101.6 kg	5.08 mL

BEQVEZ is provided in various pack sizes to accommodate the required number of vials to meet the dosing requirements for each patient based on their calculated dose weight. The number of vials per pack are provided in Table 1 along with the corresponding dosing weight bands.

Table 1. BEQVEZ Treatment Pack Sizes

Patient Dose Weight (kg)	Vial Count
≤ 55	3
>55 to ≤ 75	4
>75 to ≤95	5
>95 to ≤115	6
>115 to ≤135	7

Special populationsHepatic impairment

Patients with significant/unstable liver disease were excluded from clinical trials with BEQVEZ including patients with alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) levels greater than twice the upper limit of normal (ULN); bilirubin greater than 1.5 times the ULN, current unstable liver or biliary disease (defined by the presence of ascites, liver-related coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis), active viral hepatitis; and/or pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy. The safety and efficacy of BEQVEZ in these patients have not been established. No dose adjustments are recommended in patients with hepatic impairment should they be considered eligible for treatment with BEQVEZ. See [4.1 Dosing Considerations](#) for guidance on patient selection including the need to evaluate liver health.

Renal impairment

Patients with renal impairment defined as creatinine > 2.0 mg/dL were excluded from clinical studies. The safety and efficacy of BEQVEZ in these patients have not been established.

Geriatrics

Patients ≥ 65 years were excluded from clinical trials with BEQVEZ. The safety and efficacy of BEQVEZ in patients ≥ 65 years of age have not been established.

Pediatrics

The safety and efficacy of BEQVEZ in children and adolescents under 18 years of age have not yet been established. No data are available. Health Canada has not authorized an indication for pediatric use (see [1.1 Pediatrics](#)).

Women

BEQVEZ is not intended for administration in women.

4.4 Administration

Preparation

BEQVEZ is prepared for intravenous infusion by diluting in 0.9% sodium chloride with 0.25% human serum albumin (HSA).

Precautions to be taken before handling or administering BEQVEZ

This medicinal product contains recombinant viral vector product. Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while preparing or administering BEQVEZ.

For detailed instructions on the handling, accidental exposure to and disposal of this medicinal product, please see [12 SPECIAL HANDLING INSTRUCTIONS](#).

Preparation of diluent solution (0.9% sodium chloride with 0.25% HSA)

- HSA used for preparation of BEQVEZ must be commercially available in Canada (i.e., have a Drug Identification Number). 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 based on the patient's body weight and BMI as described in section [4.2. Recommended Dose and Dosage Adjustment](#).
- Calculate the volume of 0.9% sodium chloride 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 0.9% sodium chloride in an appropriate intravenous (IV) infusion container. Materials compatible with BEQVEZ are listed below:

Component	Material of Construction
Intravenous (IV) infusion container	Polyvinyl chloride (PVC) Ethylene vinyl acetate (EVA) Polyolefin (polyethylene and/or polypropylene)
Infusion set (line material)	Polyvinyl chloride (PVC) Polybutadiene Polyurethane Polyethylene

- 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.

Product vial thawing

- Remove BEQVEZ from the freezer.
- 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.
- Prior to use, ensure that visible ice crystals are not present in the solution.
- 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 discoloration before use. 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 of solution for infusion

- Visually inspect thawed product for particulate matter prior to administration. Do not use vials that contain visible particulates.
- The formulation does not contain a preservative and 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 invert the prepared dosing solution in the IV infusion bag to mix. Minimize foaming and do not shake vigorously. Dosing solution should be well mixed.
- The solution for infusion should be equilibrated to ambient temperature before administration to the patient.

Administration

For intravenous use.

BEQVEZ is administered as a single-dose intravenous infusion over approximately 60 minutes.

An in-line 0.2 µm PES or Nylon IV filter may be used for administration.

After the entire content of the infusion bag is infused, the infusion line should be flushed using local site procedures.

For precautions to be taken after handling or administering this medicinal product, please see [7 WARNINGS AND PRECAUTIONS – General](#).

Monitoring post-infusion

After administration of BEQVEZ, regular monitoring is required. This includes examinations of:

- Liver enzymes to monitor for liver enzyme elevations which may indicate immune-mediated liver hepatotoxicity (see [7 WARNINGS AND PRECAUTIONS](#)). Monitor ALT/AST levels by testing

twice weekly for at least 3 months following administration of BEQVEZ. See Table 2 for the recommended monitoring of liver function post-BEQVEZ infusion.

- Factor IX activity (e.g. twice weekly for at least 3 months).
 - Monitor patients regularly for their Factor IX activity (see [7 WARNINGS and PRECAUTIONS, Monitoring and Laboratory Tests](#) and Table 2).
 - Use of exogenous Factor IX concentrates before and after BEQVEZ administration may affect an accurate estimation of BEQVEZ-derived Factor IX activity.
- Perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g. annually) in patients with pre-existing risk factors for hepatocellular carcinoma (see [7 WARNINGS AND PRECAUTIONS](#)).
- Monitor patients for human Factor IX inhibitors. Post-dose testing should be performed if plasma Factor IX activity levels are not achieved, decrease or if bleeding is not controlled or returns.

Table 2. Recommended Hepatic Function (ALT and AST) and Factor IX Activity Monitoring Applied in Clinical Studies with BEQVEZ

Timeframe	Monitoring Frequency
Weeks 1 to 12	Twice weekly
Weeks 13 to 18	Weekly
Weeks 19 to 52 (Year 1)	Every 8 to 10 weeks
Year 1 to end of Year 3	Quarterly
Year 4 to end of Year 6	Every 6 months
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 minimize the impact of inter-laboratory variability.

Corticosteroid regimen

An immune response to the AAVRh74var capsid proteins will occur after BEQVEZ administration (see [14.3 Immunogenicity](#)). This may lead to elevations in liver transaminases (transaminitis) (see [7 WARNINGS AND PRECAUTIONS](#) and [8 ADVERSE REACTIONS](#)). Treatment with corticosteroids for immune-mediated hepatitis should be considered if any of the following criteria are met:

Transaminase increase

- Single increase ≥ 1.5 -fold of the baseline or $2 \times$ ULN transaminase value since the last value obtained prior to infusion.
- Consecutive increases (an increase in transaminases on 2 subsequent blood tests independent of Factor IX activity values).

Factor IX activity decrease

- In the absence of alternative etiology, a single significant decrease that could trigger the risk of bleeding.
- Consecutive decreases (a decline in Factor IX activity on 2 consecutive blood tests independent of transaminase values) particularly during the first 120 days post-infusion.

Table 3 gives the recommended tapering course of oral corticosteroids (i.e., prednisone/prednisolone) which will be the first consideration for suppression of apparent immune hepatitis. Reference to the corticosteroid product information for risks and required precautions is recommended.

Table 3. Recommended Treatment Regimen for Oral Corticosteroids Applied in Clinical Studies with BEQVEZ

Schedule (oral corticosteroid treatment regimen)	Prednisolone/Prednisone (mg/day)
Week 1	~60 to 100*
Week 2	60**
Week 3	40
Week 4	30
Week 5	30
Week 6	20***
Week 7	15
Week 8	10

* Mainly based on body weight.

** See the paragraph below this table.

*** Maintain at 20 mg/day until transaminases return to baseline, then reduce by 5 mg/day until 10 mg/day is achieved then reduce by 2.5 mg/week up to 5 mg daily.

Approximately 60 to 100 mg once a day of oral corticosteroids for the first week is recommended as the starting dose. 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.

The following schedule of combined oral corticosteroids and intravenous corticosteroids (methylprednisolone) is recommended if there is no evidence of resolution of transaminase elevation while on oral corticosteroids treatment alone (see Table 4).

Table 4. Recommended Treatment Regimen for Combination Intravenous and Oral Corticosteroids Applied in Clinical Studies with BEQVEZ

Schedule (corticosteroid treatment regimen)	Oral Prednisolone/Prednisone (mg/day)	Intravenous Methylprednisolone (g/day)
Days 1 to 3	n/a	1
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

Table 4. Recommended Treatment Regimen for Combination Intravenous and Oral Corticosteroids Applied in Clinical Studies with BEQVEZ

Schedule (corticosteroid treatment regimen)	Oral Prednisolone/Prednisone (mg/day)	Intravenous Methylprednisolone (g/day)
Week 9	5	n/a

Discontinuation of continuous routine prophylaxis with exogenous human Factor IX

It may take several weeks before improved hemostatic control becomes apparent after BEQVEZ infusion (see [10.3 Pharmacokinetics](#)). Therefore, continued hemostatic support with exogenous human Factor IX may be required during the first weeks after BEQVEZ administration to provide sufficient Factor IX coverage for the initial days post-treatment. Monitoring of the Factor IX activity (e.g. twice weekly for at least 3 months) is recommended post-dose to follow patient's response to BEQVEZ (see Table 2). In the clinical studies, a prophylactic dose of Factor IX replacement was given prior to BEQVEZ infusion.

4.5 Missed Dose

BEQVEZ is to be administered only once.

5 OVERDOSAGE

No data from clinical studies are available regarding overdose of BEQVEZ.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should record the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 5. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Concentrate for solution for infusion / 1×10^{13} vector genomes (vg)/mL	Disodium phosphate heptahydrate Monosodium phosphate monohydrate Poloxamer 188 Sodium chloride Water for injection

BEQVEZ is supplied as a concentrate for solution for infusion in a plastic vial with an elastomeric stopper and plastic snap-fit cap. It is a clear to slightly opalescent, colourless to slightly brown solution.

Each vial contains 1×10^{13} vector genomes (vg) of fidanacogene elaparvovec in an extractable volume of 1 mL. BEQVEZ requires dilution prior to administration. BEQVEZ is a sterile solution and contains no preservative.

7 WARNINGS AND PRECAUTIONS

General

Precautions to be taken after handling or administering the medicinal product

BEQVEZ may be transmitted to persons other than the patient receiving the treatment through patient excretions and secretions (see [10.3 Pharmacokinetics](#)). Vector shedding of intravenously administered AAV-based gene therapies such as BEQVEZ can occur in blood, semen, urine, feces, and saliva. To minimize 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. Barrier contraception is recommended for 1 year after BEQVEZ administration for males and their female partners of child-bearing potential (see [7 WARNINGS AND PRECAUTIONS - Reproductive Health: Female and Male Potential](#)). Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during and after treatment with BEQVEZ (see [12 SPECIAL HANDLING INSTRUCTIONS](#)).

Blood, organ and tissue donation

Advise BEQVEZ-treated patients not to donate blood, organs, tissues and cells for transplantation to minimize the risk of exposure to non-target individuals.

Driving and Operating Machinery

Patients treated with BEQVEZ may experience symptoms shortly after BEQVEZ administration that may affect their ability to drive and use machines. Patients should not drive or use machines until symptoms resolve.

Hematologic

Risk of Thromboembolic Events

In clinical studies with BEQVEZ, treatment-related thromboembolic events were not reported and there was no evidence of supraphysiological FIX activity.

Restoration of Factor IX activity following administration of BEQVEZ, which encodes for a hyperactive IX variant (Padua), may give rise to the potential risk for thromboembolic events. This potential risk is increased in Hemophilia B patients with pre-existing risk factors for thromboembolic events such as a history of cardiovascular disease, arteriosclerosis, hypertension, diabetes, and advanced age.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hemophilia B patients with ALT, AST and ALP > 2X upper limit of normal (ULN), bilirubin $\geq 1.5 \times$ ULN, unstable liver or biliary disease (defined by the presence of ascites, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis), active viral hepatitis, and/or pre-existing

diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy were excluded from clinical studies with BEQVEZ. There should be careful consideration before administering BEQVEZ to these patients (see [4.1 Dosing Considerations](#)).

Patients treated with BEQVEZ can develop liver transaminase elevations (transaminitis) (see [8 ADVERSE REACTIONS](#)). Transaminitis, particularly when observed in the first 4 months after BEQVEZ administration, is presumed to occur due to immune-mediated injury of transduced hepatocytes and can reduce therapeutic efficacy of the AAV-vector based gene therapy. In clinical studies with BEQVEZ, most subjects had asymptomatic, and predominantly mild elevations in transaminases most often within 120 days after BEQVEZ administration (see [8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data](#)).

To mitigate the risk of hepatotoxicity, monitor transaminases and Factor IX activity levels at baseline and twice weekly in the first 3 months following the administration of BEQVEZ (see Table 2 in [4.4 Administration](#)). Consider corticosteroid treatment if liver enzyme elevations are observed and/or reductions in Factor IX activity (see [4.4 Administration](#)). In clinical trials with BEQVEZ, patients requiring treatment with corticosteroids post-BEQVEZ infusion had numerically lower transgene FIX activity compared to patients who were not treated with corticosteroids (see [10.2 Pharmacodynamics](#)).

Follow-up monitoring of transaminases in all patients who developed liver enzyme elevations is recommended on a regular basis until liver enzymes return to baseline (see [4.4 Administration](#)).

Advise patients who are to be treated with BEQVEZ to avoid concomitant use of hepatotoxic medicinal substances, herbal supplements, and/or alcohol, as the efficacy of BEQVEZ could be reduced, and the risk of serious hepatic reactions may increase following BEQVEZ administration.

Hepatocellular carcinogenicity

There is a theoretical risk of hepatocellular carcinoma development resulting from the integration of liver-targeting AAV vector DNA into the genome. BEQVEZ is composed of a non-replicating AAVrh74var vector whose DNA remains largely in episomal form although DNA integration events have been reported in non-clinical studies (see [16 NON-CLINICAL TOXICOLOGY](#)).

It is recommended that patients with pre-existing risk factors for hepatocellular carcinoma (such as hepatic cirrhosis, advanced hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) receive regular abdominal ultrasound screenings and are regularly monitored (e.g. annually) for alpha-fetoprotein (AFP) elevations in the 5 years following administration (see [4.1 Dosing Considerations](#)).

Immune

Pre-existing immunity against AAVrh74var

In AAV-vector based gene therapies, pre-existing neutralizing AAV antibodies may impede transgene expression at desired therapeutic levels. Anti-AAVRh74var antibody formation can take place after exposure to a virus that is similar to the vector. All patients must be tested for the presence of anti-AAVRh74var neutralizing antibodies prior to infusion with BEQVEZ (see [4.1 Dosing Considerations](#)). It is recommended that patients should be dosed as close as possible (e.g., within approximately 8 weeks) following antibody testing confirming the absence of AAVrh74var neutralizing antibodies. Only patients negative for pre-existing anti-AAVRh74var neutralizing antibodies are eligible to receive BEQVEZ (see [1 INDICATIONS](#) and [4.1 Dosing Considerations](#)).

Infusion-related reactions

No acute hypersensitivity reactions or infusion-related reactions related to BEQVEZ were observed at the recommended dose.

Infusion related reactions, including hypersensitivity reactions and anaphylaxis, are possible following BEQVEZ administration. To minimize the risk of acute hypersensitivity reactions, closely monitor patients for signs and symptoms of infusion reactions throughout the infusion and for at least 3 hours post-infusion. Inform patients of the early and delayed symptoms and signs of hypersensitivity reactions and advise them to contact their physician and/or seek immediate emergency care if they experience any of these symptoms. In the event of an infusion reaction during administration, immediately pause and evaluate if discontinuation and/or the administration of appropriate treatment is needed. If infusion is paused, it may be restarted at a slower rate at healthcare provider discretion and based upon patient tolerability.

Monitoring and Laboratory Tests

Baseline laboratory testing is required before administration of BEQVEZ (see [4.1 Dosing Considerations](#)). After BEQVEZ administration, a patient's Factor IX activity should be regularly monitored (see [4.4 Administration](#)).

Factor IX activity assays

A field study was conducted to investigate the variability in the range of values for Factor IX activity determined by laboratories at different sites using standard protocols, commercially available assay reagents, and instruments, to measure Factor IX activity in plasma from trial participants treated with fidanacogene elaparvovec. The results indicate inter-laboratory variability across the different one-stage reagents, with greater variability observed in samples with lower Factor IX activity levels (0.025 IU/mL). Furthermore, while all assay types were able to measure transgene derived Factor IX activity, the study demonstrated inter-assay differences in absolute Factor IX activity values with consistently higher FIX activity reported with silica-based one-stage assays when compared to one-stage assays using different activators/instruments or chromogenic assays. These results agree with publications that reported on Factor IX assay discrepancies in the setting of liver-directed gene therapy and also with the results observed in clinical trials of BEQVEZ (see Table 8 in [10.2 Pharmacodynamics](#)).

It is recommended that patients' Factor IX activity be monitored using the same assay format and the same laboratory over time. This is of particular importance during the timeframe for corticosteroid treatment decision making since changes in laboratory/assay format could erroneously suggest decreasing Factor IX activity.

Monitor patients through appropriate clinical observations and laboratory tests for the development of inhibitors to Factor IX after BEQVEZ administration. Perform an assay that detects Factor IX inhibitors if bleeding is not controlled, or plasma Factor IX activity levels decrease. If Factor IX activity decreases in the absence of FIX inhibitors, then loss of transgene expression in the liver should be suspected.

Perioperative Considerations

Management in the perioperative setting

Factor IX concentrates/hemostatic agents may be used in case of invasive procedures, surgery, trauma, or bleeds in accordance with current treatment guidelines for the management of hemophilia, and based on the patient's current Factor IX activity levels.

Reproductive Health: Female and Male Potential

- **Fertility**

No information is available on the effects of BEQVEZ on female or male fertility.

Contraception after administration to males

In semen the maximum observed time for full vector DNA clearance (defined as 3 consecutive measurements below the limit of quantification) was 154 days. Male patients should be advised to be abstinent or use barrier contraception for 1 year after receiving BEQVEZ (see [10.3 Pharmacokinetics](#)).

Women of childbearing potential

No dedicated animal fertility/embryofetal studies have been conducted. As BEQVEZ has not been studied in women, it is currently not recommended in this population.

7.1 Special Populations

7.1.1 Pregnant Women

BEQVEZ is not intended for administration in women and no women were enrolled in clinical studies with BEQVEZ.

7.1.2 Breast-feeding

BEQVEZ is not intended for administration in women and no women were enrolled in clinical studies with BEQVEZ.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The safety and efficacy of BEQVEZ in patients ≥ 65 years of age have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of BEQVEZ was evaluated in 60 patients who received a single intravenous dose of 5×10^{11} vector genomes/kg in 2 open-label clinical studies. The most frequently reported adverse reaction (incidence $\geq 5\%$) related to BEQVEZ in clinical trials (N=60) was transaminases increased (46.6%) (based on the following combined preferred terms: alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, hepatic enzyme increased, hepatic function abnormal, liver function test abnormal, hypertransaminasemia, hepatotoxicity and transaminases increased) (see [8.4 Abnormal Laboratory Findings, Clinical Findings, and Other Quantitative Data](#)). Serious adverse reactions related to BEQVEZ administration were anemia and duodenal ulcer hemorrhage in one patient after receiving corticosteroid treatment without gastric acid prophylaxis for the management of transaminase increases. For all treatment emergent adverse events ($\geq 5\%$) refer to Table 6.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 6. Treatment Emergent Adverse Events (All Causalities, ≥5%) Following Treatment with BEQVEZ

MedDRA System Organ Class (SOC) Treatment Emergent Adverse Events	BEQVEZ N=60 n (%)
Blood and lymphatic system disorders	
Anemia	3 (5.0%)
Gastrointestinal disorders	
Abdominal pain ^a	8 (13.3%)
Diarrhea	3 (5.0%)
Dyspepsia	3 (5.0%)
Gastrointestinal reflux disease	3 (5.0%)
Hepatobiliary disorders	
Hepatic steatosis	3 (5.0%)
Infections and infestations	
Nasopharyngitis	11 (18.3%)
Upper respiratory tract infection	9 (15.0%)
COVID-19	6 (10.0%)
Gastroenteritis	3 (5.0%)
Injury, poisoning and procedural complications	
Ligament sprain	3 (5.0%)
Muscle strain	3 (5.0%)
Investigations	
Transaminases increased ^b	28 (46.6%)
Coagulation Factor IX level decreased	3 (5.0%)
SARS-CoV-2 test positive	3 (5.0%)
Musculoskeletal and connective tissue disorders	
Arthralgia	9 (15.0%)
Arthropathy ^c	6 (10.0%)
Back pain	4 (6.7%)
Joint swelling	3 (5.0%)
Myalgia	3 (5.0%)
Pain in extremity	3 (5.0%)
Nervous system disorders	
Headache ^d	10 (16.6%)
Dizziness	3 (5.0%)
Psychiatric disorders	
Insomnia	4 (6.7%)
Respiratory, thoracic and mediastinal disorders	

Table 6. Treatment Emergent Adverse Events (All Causalities, ≥5%) Following Treatment with BEQVEZ

MedDRA System Organ Class (SOC) Treatment Emergent Adverse Events	BEQVEZ N=60 n (%)
Cough ^e	3 (5.0%)
Skin and subcutaneous tissue disorders	
Acne	3 (5.0%)
Vascular disorders	
Hypertension	3 (5.0%)

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort

^b Includes alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, hepatic enzyme increased, hepatic function abnormal, liver function test abnormal, hypertransaminasemia, hepatotoxicity and transaminases increased

^c Includes arthropathy, hemophilic arthropathy, joint range of motion decreased, joint stiffness

^d Includes headache, tension headache, sinus headache

^e Includes cough, productive cough

For additional information, please refer to [8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data](#).

8.3 Less Common Clinical Trial Adverse Reactions

Cardiac disorders: angina pectoris (1.7%), palpitations (3.3%)

Hepatobiliary disorders: drug induced liver injury (1.7%), hepatitis (1.7%), liver disorder (1.7%)

Skin and subcutaneous tissue disorders: rash (1.7%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hepatic laboratory abnormalities

Table 7 describes hepatic laboratory abnormalities following administration of BEQVEZ. Elevated transaminases may indicate the need to initiate corticosteroid treatment (see [4.4 Administration](#) and [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

Table 7. Hepatic Laboratory Abnormalities in Patients Administered 5×10^{11} vg/kg Body Weight BEQVEZ in Clinical Studies

Laboratory Parameter Increases ^a	BEQVEZ N = 60 N (%)
ALT increases > ULN^b	31 (51.7%)
> ULN – 3.0 x ULN ^c	26 (43.3%)
> 3.0 - 5.0 x ULN ^d	5 (8.3%)
AST increases > ULN^b	24 (40.0%)

Table 7. Hepatic Laboratory Abnormalities in Patients Administered 5×10^{11} vg/kg Body Weight BEQVEZ in Clinical Studies

Laboratory Parameter Increases ^a	BEQVEZ N = 60 N (%)
> ULN – 3.0 x ULN ^c	21 (35.0%)
> 3.0 - 5.0 x ULN ^d	1 (1.7%)
> 5.0 – 20.0 x ULN ^e	2 (3.3%)
Bilirubin increases > ULN^b	5 (8.3%)
> ULN – 1.5 x ULN ^c	5 (8.3%)

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

^aHighest post-dose CTCAE Grades of values are presented

^bNot all patients with laboratory abnormality >ULN reached CTCAE Grade 1 due to elevated baseline levels

^cCTCAE Grade 1

^dCTCAE Grade 2

^eCTCAE Grade 3

8.5 Post-Market Adverse Reactions

Not Applicable

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interaction studies have been performed.

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

9.4 Drug-Drug Interactions

Drug-drug interactions have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fidanacogene elaparvovec is a gene therapy designed to introduce a functional copy of a high activity variant of the Factor IX gene (FIX-R338L) into hepatocytes to address the cause of Hemophilia B.

Fidanacogene elaparvovec is a non-replicating recombinant AAV vector that utilizes the AAVRh74var capsid to deliver a functional human Factor IX transgene. The AAVRh74var capsid is derived from the Rh74 AAV, which is not known to cause disease in humans. 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. Expression of the transgene is driven by a liver specific promoter, which results in tissue specific expression. As a result, BEQVEZ helps to restore circulating Factor IX procoagulant activity and hemostatic potential in patients with Hemophilia B, which may limit bleeding episodes and the need for exogenous Factor IX treatment.

10.2 Pharmacodynamics

Factor IX Activity

The mean and median Factor IX activity observed after administration of fidanacogene elaparvovec is shown over time in Table 8. In the pivotal study C0371002, 45 patients with historical Factor IX activity <2% received fidanacogene elaparvovec. The participants' FIX activities were measured over time by each of 3 assays (i.e., SynthAsil Reagent one-stage assay, Actin-FSL reagent one-stage assay, and chromogenic assay). The silica based (SynthAsil) assay consistently gave higher FIX activity values than either the one-stage actin-FSL assay or the chromogenic assay.

Table 8. C0371002 Study: Factor IX Activity Over Time by Assay

	One-Stage Assay (Silica-based)* (N=45)	One-Stage Assay (Actin-FSL Reagent) (N=45)	Chromogenic Assay (N=45)
Week 12			
N	44	43	44
Mean (SD)	27.8 (15.23)	13.5 (8.13)	13.9 (9.30)
Median (Min, Max)	26.5 (3.2, 68.6)	13.5 (1.7, 35.1)	12.1 (1.4, 36.3)
Month 6			
n	39	41	40
Mean (SD)	27.7 (21.34)	13.1 (11.14)	14.8 (12.96)
Median (Min, Max)	23.2 (1.9, 99.7)	10.1 (0.6, 55.0)	10.3 (1.0, 57.7)
Month 15			
N	35	34	35
Mean (SD)	27.5 (25.74)	13.1 (12.79)	15.8 (17.00)
Median (Min, Max)	23.3 (1.9, 119.0)	10.3 (1.8, 62.0)	10.2 (1.9, 74.2)

Any samples taken within 7 days (14 days if extended half-life product is used) of exogenous 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%.

* SynthAsil Reagent

Table 8. C0371002 Study: Factor IX Activity Over Time by Assay

From week 12 to month 15, the levels of Factor IX remained relatively stable. At month 15, 86% patients (30 out of 35) were in or above the mild range (Factor IX activity >5%) based on Factor IX activity measured using the one-stage SynthAsil assay, and 68% and 71% were in or above the mild range based on one-stage Actin-FSL assay and chromogenic assay, respectively.

In the supportive studies C0371005/1003, Factor IX activity (without imputation) remained stable over time (up to 6 years), with mean Factor IX activity (One-stage Assay with Actin-FSL reagent) at 27.9% at Month 15 (n=9), 24.9% at Month 24 (n=14), 21.5% at Month 48 (Year 4, n=11) and 21.5% at Month 72 (Year 6, n=5). No patient had resumed FIX prophylaxis post-BEQVEZ infusion.

Overall in the clinical studies, thirty-one out of 60 (51.7%) patients received corticosteroids based on investigator discretion leveraging guidance provided in the protocol. In the pivotal study C0371002, twenty-eight out of 45 (62.2%) patients received corticosteroids due to liver enzyme elevations and/or a reduction in Factor IX activity. The mean time to corticosteroid initiation was 45 days (range: 11, 123). The mean duration of corticosteroid treatment was 113 days (range: 41, 276 days). Hemophilia B patients treated with BEQVEZ who received corticosteroids had numerically lower steady state (geometric mean of FIX activity from week 12 to month 15) Factor IX activity compared to Hemophilia B patients treated with BEQVEZ who did not require corticosteroids [see [7 Warnings and Precautions - Hepatic/Biliary/Pancreatic](#)]. Steady state Factor IX activity by corticosteroid use (yes, n=28; no, n=17) after receiving BEQVEZ are shown in Table 9.

Table 9. C0371002 Study: Steady State Factor IX Activity (Week 12 to Month 15) by Corticosteroid Use and by Assay

	Factor IX Activity in %	
	Without Corticosteroids (N=17)	With Corticosteroids (N=28)
One-Stage Assay (Silica-based)*		
Mean (SD)	32.0 (18.78)	22.2 (14.75)
Median (Q1, Q3)	28.3 (23.5, 33.8)	20.1 (10.0, 32.4)
One-Stage Assay (Actin-FSL Reagent)		
Mean (SD)	15.8 (9.66)	10.7 (8.01)
Median (Q1, Q3)	13.9 (10.7, 17.6)	8.4 (3.8, 15.5)
Chromogenic Assay		
Mean (SD)	16.8 (11.57)	11.5 (9.29)
Median (Q1, Q3)	12.6 (9.4, 21.2)	8.9 (4.6, 17.4)

Any samples taken within 7 days (14 days if extended half-life product is used) of exogenous 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%.

Steady state FIX:C is calculated for each participant as geometric means of all eligible FIX:C measures from 12 weeks to 15 months after IP infusion.

* SynthAsil Reagent

10.3 Pharmacokinetics

Shedding of BEQVEZ vector DNA was evaluated and occurred in the blood, semen, saliva and urine of treated patients. Although the vector DNA remains largely episomal, events of integration into the genome have been observed in non-clinical studies in non-human primates and therefore there is a potential risk to human health.

Fidanacogene elaparvovec vector DNA levels were measured in studies C0371002 and C0371005/1003 and quantified in blood (peripheral blood mononuclear cells, serum/plasma), saliva, semen and urine using a quantitative polymerase chain reaction (qPCR) assay. The assay is sensitive and specific to fidanacogene elaparvovec vector DNA including fidanacogene elaparvovec DNA fragments and does not indicate whether DNA is present in the vector capsid, in cells or in the fluid phase of the matrix (e.g., blood plasma, seminal fluid) or whether intact vector is present.

Clinical pharmacokinetics and shedding

Vector shedding after infusion with BEQVEZ was assessed in 60 patients at multiple time points in clinical studies. 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 2 weeks after infusion. Highest peak vector DNA concentrations were found in serum/plasma compared to the other liquid matrices (saliva, urine, semen). Clearance of vector DNA was defined as having 3 consecutive results below the limit of quantification (LOQ). Based on this definition, vector DNA was cleared from serum, plasma, saliva, and semen within means of 3, 3, 1.5, and 3 months post-infusion, respectively. PBMC were slowest to clear vector DNA with an observed mean of 12 months. In semen, the maximum observed time for vector DNA to clear was 154 days.

Nonclinical biodistribution

In a monkey biodistribution study, 22 tissues were collected at 30 and 92 days following treatment. The highest levels of vector DNA were found in liver with levels approximately 20-fold higher than in spleen, the organ with the second most abundant levels of genomic DNA. There was very little biodistribution to testes.

Pharmacokinetics in special populations

No pharmacokinetic studies using BEQVEZ have been conducted in special populations.

11 STORAGE, STABILITY AND DISPOSAL

Store at –90 °C to –60 °C and transport at –100 °C to –60 °C.

Immediately following receipt, original packages removed from frozen transport packaging (–100 °C to –60 °C) may be stored at room temperature (up to 30 °C) for up to 5 minutes during transfer.

Store upright in the original package and avoid direct sunlight and ultraviolet light exposure. If cartons or individual vials are tipped over or inverted during storage and handling, place the carton or individual vials back in the upright orientation immediately.

After thawing, do not refreeze.

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** (15°C to 30°C) between removing vials from frozen storage until the beginning of dose preparation should be no more than 3 hours.

Once thawed, the vial may be stored refrigerated at 2 °C to 8 °C in the inner carton for up to 24 hours.

The thawed vial cannot be re-frozen.

Diluted Solution for Infusion

Following dilution in 0.9% sodium chloride with 0.25% human serum albumin, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 30 °C. However, the prepared dose should be administered as soon as possible.

Special Precautions for Disposal

This medicinal product contains recombinant viral vector product.

Unused medicinal product and all materials (solid and liquid waste) that have been in contact with the recombinant viral vector product should be handled and disposed of as potentially infectious waste in a container dedicated to biohazard material, autoclaved and destroyed in accordance with local biosafety guidelines.

Non-disposable materials should be cleaned with a disinfectant with proven virucidal activity for nonenveloped viruses e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm) after usage and then autoclaved, if possible. Contact surfaces should be disinfected with a similar disinfectant.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned under [4.4 Administration](#).

12 SPECIAL HANDLING INSTRUCTIONS

Precautions to be taken before handling or administering BEQVEZ

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

This medicinal product contains recombinant viral vector product.

Appropriate precautions for the handling, disposal or accidental exposure of BEQVEZ should be followed:

- BEQVEZ should be handled aseptically under sterile conditions.
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves, and masks) should be worn while handling or administering BEQVEZ. Personnel should not work with BEQVEZ if their skin is cut or scratched.
- All work surfaces which have potentially been in contact with BEQVEZ must be decontaminated with an appropriate disinfectant with proven virucidal activity for non-enveloped viruses (e.g., wiped with an absorbent gauze pad using a bleach solution followed by alcohol wipes).
- All 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 accordance with

local guidelines for handling of biological waste. All clean-up materials must be double bagged and disposed of per local guidelines for handling of biological waste.

- 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 for at least 15 minutes.
 - In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.
 - In case of accidental needle stick exposure, encourage bleeding of the wound and wash injection area well with soap and water.
 - In case of accidental inhalation, move the person into fresh air.
 - In case of accidental oral exposure, abundantly rinse mouth with water.
 - In each case, obtain subsequent medical attention.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Fidanacogene elaparvovec

Structural formula: Fidanacogene elaparvovec is an adeno-associated viral (AAV)-based gene therapy that consists of a recombinant viral capsid (AAVRh74var) derived from a naturally occurring AAV serotype (Rh74) packaging genome containing the human coagulation Factor IX (FIX) transgene modified to a high-specific Factor IX activity variant known as FIX-R338L.

Physicochemical properties: Clear to slightly opalescent, colourless to slightly brown solution

Product Characteristics:

Fidanacogene elaparvovec is a non-replicating recombinant AAV vector serotype Rh74var containing a codon-optimized coding DNA sequence to deliver human coagulation Factor IX variant R338L (Padua) under the control of a liver promoter (ApoE/haAT). It is produced by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adult Hemophilia B Patients without FIX Inhibitors

Table 10. Summary of Patient Demographics for Pivotal Clinical Trial in Hemophilia B

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
C0371002 (Phase 3)	Open-label, single-arm, single dose, multi-center trial	Single IV infusion of 5×10^{11} vg/kg	45	33.18 (18, 62) years	Male (100%)

Study Results

The efficacy of BEQVEZ was evaluated in an ongoing open-label, single-dose, single-arm, multi-site study (C0371002). The study enrolled 45 adult male patients aged 18 to 62 years (at time of infusion) with moderately severe to severe Hemophilia B (Factor IX activity $\leq 2\%$). Eligible patients received a single intravenous infusion dose of BEQVEZ at 5×10^{11} vg/kg of body weight. For participants with BMI >30 kg/m², the dose was calculated based on an adjusted body weight determination that assumes a maximum permissible BMI of 30 kg/m². Prior to infusion, all patients completed a lead-in study of at least 6 months with standard of care Factor IX prophylaxis.

Trial eligibility required all patients to be screened for neutralizing antibodies to AAVRh74var using a cell-based antibody-mediated neutralization assay. Patients who were positive for neutralizing antibodies (titer $\geq 1:1$) were excluded from the trial resulting in the exclusion of 61.1% of screened

patients. Patients were also excluded from the study if they were < 18 and > 65 years of age, had prior history of Factor IX inhibitor or positive Factor IX inhibitor test results at screening, active hepatitis B or C infection, ALT, AST, or ALP > 2 × ULN, bilirubin > 1.5 × ULN, unstable liver or biliary disease defined by the presence of ascites, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis, significant liver fibrosis or significant liver disease (defined as portal hypertension, splenomegaly and hepatic encephalopathy), creatinine > 2.0 mg/dL, platelets < 100000 cells/mcL and HIV infection with either CD4+ cell count ≤ 200 mm³ or viral load > 20 copies/mL. Thirty-three of 45 (73.3%) patients were White, 7 (15.6%) were Asian, 1 (2.2%) were Black or African American and 4 (8.9%) were not reported.

The primary efficacy endpoint was the Annualized Bleeding rate (ABR) for total bleeds (ABR_{total}; treated and untreated) from Week 12 to Month 15 versus usual care Factor IX prophylaxis replacement regimen, comparing pre- and post-BEQVEZ infusion.

The key secondary endpoints were ABR for treated bleeds (ABR_{treat}) and the annualized infusion rate (AIR) of exogenous Factor IX from Week 12 to Month 15.

Five out of 45 (11.1%) patients resumed Factor IX prophylaxis during Week 12 to Month 15 post-BEQVEZ infusion. In addition, as permitted by the protocol, six patients received exogenous Factor IX injections (ranging from 1 to 9 injections each) prior to a planned physical activity with a high risk of injury (e.g., surgery or sporting activity) during Week 12 to Month 15 following BEQVEZ infusion.

The efficacy results of BEQVEZ are shown in Table 11. Non-inferiority of BEQVEZ treatment was demonstrated as the upper bound for the 95% confidence interval of the treatment difference in ABR_{total} (post-BEQVEZ - lead-in prophylaxis) is lower than the pre-specified non-inferiority margin of 3.

Table 11. C0371002 Study: Annualized Bleed Rate and Annualized Factor Infusions

	Factor IX Prophylaxis^a (N=45)	BEQVEZ^b (N=45)
ABR_{total}^{c,d}		
n (%) of patients without any bleeds	13 (28.9)	29 (64.4)
Model-based estimate (95% CI)	4.51 (1.85, 7.17)	2.17 (0.64, 3.70)
Treatment difference (post-BEQVEZ - lead-in prophylaxis) (95% CI)		-2.34 (-4.97, 0.29)
ABR_{treat}^c		
n (%) of patients without any bleeds	16 (35.6)	33 (73.3)
Model-based estimate (95% CI)	3.35 (1.71, 4.98)	0.73 (0.25, 1.21)
Treatment difference (post-BEQVEZ - lead-in prophylaxis) (95% CI)		-2.62 (-4.27, -0.96)
Spontaneous Bleeding		
n (%) of patients without any bleeds	18 (40.0)	35 (77.8)
Joint Bleeding		
n (%) of patients without any bleeds	20 (44.4)	31 (68.9)
AIR		

Table 11. C0371002 Study: Annualized Bleed Rate and Annualized Factor Infusions

	Factor IX Prophylaxis^a (N=45)	BEQVEZ^b (N=45)
n (%) of patients without any infusions	0	29 (64.4)
Mean (SD)	58.83 (29.06)	4.46 (10.03)
Treatment difference (post-BEQVEZ - lead-in prophylaxis) (95% CI)		-54.37 (-63.64, -45.10)

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

ABR_{treat} = Annualized Bleed Rate for treated bleeds (treated with Factor IX, excluding procedural bleeds).

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

CI= confidence Interval

^alead-in prophylaxis

^bPost-infusion period is defined from Week 12 to Month 15 post-infusion of BEQVEZ to ensure that this period represented steady-state Factor IX expression from the transgene.

^cModel-based ABR estimates and p-value for treatment difference are obtained from a repeated measures generalized linear model (GLM) with negative binomial distribution and identity link function. The model accounts for the paired design of the study by including durations of pre- and post-infusion periods as a parameter.

^d5 subjects who resumed Factor IX prophylaxis from the date of resumption to Month 15 were multiply imputed using a negative binomial distribution under a conservative assumption of mean ABR_{total} of 20 (equivalent to bleeding counts during on-demand treatment) with a dispersion parameter of 0.5 to reflect high variability in bleeding counts under on-demand treatment.

14.3 Immunogenicity

A sustained increase in neutralizing anti-AAVRh74var antibodies has been observed after administration of BEQVEZ in all subjects who participated in clinical studies and had neutralizing antibody (nAb) assessment.

No patients developed Factor IX inhibitors during the clinical studies using BEQVEZ. There are currently no data regarding the efficacy of BEQVEZ when used in patients with a history of Factor IX inhibitors. Patients with Factor IX inhibitors should not receive BEQVEZ.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

No adverse findings were observed in a 92-day single-dose intravenous general toxicity study in cynomolgus monkeys at doses up to 5×10^{12} vg/kg.

Carcinogenicity:

Carcinogenicity studies have not been conducted with BEQVEZ.

Genotoxicity:

Genotoxicity studies have not been conducted with BEQVEZ.

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 (only liver samples were evaluated) resulted in altered liver function, or hepatocellular hyperplasia and carcinoma. The integration profile was considered low risk as the integrations were mostly uniformly distributed throughout the genome (enrichment observed in chromosome 7 and 19), with common insertion sites identified. There was minimal evidence of potential clonal expansion.

Reproductive and Developmental Toxicology:

Reproductive toxicity and impairment of fertility studies have not been conducted with BEQVEZ.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBEQVEZ™

Fidanacogene elaparvovec

Read this carefully before you receive **BEQVEZ**. This leaflet is a summary and will not tell you everything about this medicine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BEQVEZ**.

What is BEQVEZ used for?

BEQVEZ is used to treat people with Hemophilia B who have a gene that is not functioning to allow the body to make enough of a protein called Factor IX. This protein is important for blood to clot and stop bleeding. **BEQVEZ** is given to help make enough working Factor IX protein to help prevent bleeding in patients with Hemophilia B.

How does BEQVEZ work?

BEQVEZ is a type of medicine called a ‘gene therapy.’ The active substance in **BEQVEZ**, fidanacogene elaparvovec, is based on a virus that does not cause disease in humans. This virus cannot spread in the body but can deliver a copy of the Factor IX gene into your cells. This allows the body to produce Factor IX protein and increase the levels of working Factor IX in the blood to help the blood to clot and prevent or reduce bleeding episodes in patients with Hemophilia B.

What are the ingredients in BEQVEZ?

Medicinal ingredient: fidanacogene elaparvovec

Non-medicinal ingredients: disodium phosphate heptahydrate, monosodium phosphate monohydrate, poloxamer 188, sodium chloride, water for injection.

This medicine contains recombinant adeno-associated viral vectors.

BEQVEZ comes in the following dosage forms:

BEQVEZ is supplied in a plastic vial. When thawed, **BEQVEZ** is a clear to slightly opalescent, colourless to slightly brown solution.

Do not use BEQVEZ if:

- You are allergic to fidanacogene elaparvovec or to any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given BEQVEZ. Talk about any health conditions or problems you may have, including if you:

- Have or had liver or kidney problems
- Have an infection
- Are planning on having children

For your personal safety, the treatment with **BEQVEZ** will take place under the supervision of your healthcare professional in a clinical setting.

Before treatment with BEQVEZ

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

- Antibody blood tests: Your healthcare professional will conduct blood tests to check for certain antibodies (proteins) before treatment with BEQVEZ, including:
 - Blood tests to see if you have antibodies directed against the type of virus used to make BEQVEZ. If you have these antibodies, you will not receive BEQVEZ.
 - Blood tests to check for the presence of antibodies in your blood directed against the human Factor IX protein (Factor IX inhibitors). If you test positive for these antibodies, another test will be performed in approximately 2 weeks. If both the initial test and re-test results are positive, you will not receive BEQVEZ.
- Liver health: If you have poor liver health you may not receive BEQVEZ. Your healthcare professional will check the status of your liver health before you start treatment with BEQVEZ and perform:
 - Blood tests to check your liver enzymes in your blood
 - Liver ultrasound
 - Tests to check for scarring or thickening of your liver (fibrosis assessment).

During or shortly after receiving BEQVEZ

- Infusion-related side effects can occur during or shortly after you are given BEQVEZ infusion (drip). Your healthcare professional will monitor you during BEQVEZ infusion and for at least 3 hours after. You may experience symptoms such as, but not limited to, hypotension (low blood pressure), fever, palpitation (fast or irregular heartbeat), nausea, vomiting, chills or headache. Tell your healthcare professional **immediately** if you experience these or any other symptoms during or shortly after the treatment infusion.
- Depending on your symptoms, your infusion may be interrupted. If the infusion is interrupted, your healthcare professional may choose to restart it at a slower rate. Your healthcare professional may also consider if you should be given another medicine to help manage your symptoms.

After treatment with BEQVEZ

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

- Liver enzymes: BEQVEZ will trigger a response within your immune system that could lead to an increased level of certain liver enzymes in your blood called transaminases (transaminitis). Your healthcare professional will regularly monitor your liver enzyme levels to ensure that the medicine is working as it should:
 - In the first 3 months you will have blood tests twice per week to monitor your liver enzyme levels.
 - If you experience an increase in liver enzymes, you may have more frequent blood tests to check the levels of your liver enzymes, until they return to normal. You may also need to take another medicine (corticosteroids) to manage these side effects. Corticosteroids may cause side effects when you take

them and your healthcare professional may adjust your dosage regularly depending on your blood test results.

- Your healthcare professional may also perform additional tests to exclude other causes for the increase in your liver enzymes, if needed, in consultation with a healthcare professional experienced in liver diseases (hepatologist).
- Your healthcare professional will continue to regularly monitor your liver enzyme levels over time following BEQVEZ administration.
- Factor IX levels: Your healthcare professional will regularly check your Factor IX levels to see if treatment with BEQVEZ was successful.
 - In at least the first 3 months after you are given BEQVEZ, you will have blood tests twice per week to check your Factor IX levels. Your healthcare professional will continue to monitor your Factor IX levels at regular intervals over time following BEQVEZ administration.

Discontinuation of other Hemophilia B treatments:

Talk to your healthcare professional about if or when you should stop your other Hemophilia B treatments and develop a treatment plan of what to do in case of surgery, trauma, bleeds, or any procedures that will increase your risk of bleeding. It is important to continue your monitoring and keep your healthcare professional visits.

Risk of liver cancer (hepatocellular carcinoma) potentially associated with BEQVEZ

BEQVEZ will insert into cells in your body and it could possibly insert into your DNA. This could contribute to a risk of cancer, such as liver cancer. Although there is no evidence of this in the clinical trials so far, this remains possible because of the nature of the medicine. You should therefore discuss this with your healthcare professional.

If you are a patient with risk factors for liver cancer (you have liver cirrhosis or scarring and thickening of the liver, or Hepatitis B, Hepatitis C or fatty liver), your healthcare professional will monitor your liver health yearly for at least 5 years after BEQVEZ administration and perform the following tests:

- Annual liver ultrasound
- Annual blood tests to check for increases in protein (alpha-fetoprotein).

Avoiding blood donations and donations for transplantations

To ensure BEQVEZ DNA is not transferred from you to another person, you will not be able to donate blood, organs, tissues, or cells after you have been treated with BEQVEZ.

Abnormal clotting of blood (thromboembolic events)

After treatment with BEQVEZ, your Factor IX protein level may increase. Although not observed in clinical trials with BEQVEZ, Factor IX protein could increase to levels above the normal range. Unusually high Factor IX levels may cause your blood to clot abnormally, increasing the risk of blood clots. You may be at increased risk for abnormal blood clotting if you have pre-existing problems with your heart and blood vessels (e.g., a history of heart disease, high blood pressure, or if you are diabetic). Your healthcare professional will regularly monitor your blood for potential abnormalities in Factor IX levels. Consult your doctor immediately, if you observe signs of abnormal clotting, such as sudden chest pain, shortness of breath, sudden onset of muscle weakness, loss of sensation and/or balance, decreased alertness, difficulty in speaking, or swelling of one or both legs.

Receiving gene therapy again in the future

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

Long-term follow-up

After receiving this treatment, you are expected to be enrolled in a registry to follow Hemophilia patients. This is to help understand the long-term safety and how well it continues to work.

Other warnings you should know about:

- Children and adolescents: BEQVEZ is not recommended for children or adolescents under the age of 18.
- Pregnancy, breast-feeding and fertility: BEQVEZ is not intended for use in women and there are no data regarding BEQVEZ in pregnant or breast-feeding women. There is no information on the effect of BEQVEZ on female or male fertility.
- Driving and using machines: Some side effects of BEQVEZ may affect your ability to drive or use machines. You should wait until the side effects go away before you drive or use machines.
- Hygiene precautions after receiving BEQVEZ: The active substance in BEQVEZ may be transmitted to persons other than the patient receiving the treatment through blood, semen and other bodily waste and fluids; this is called 'shedding'. You, and your caregivers, should take precautions and should practice proper hand hygiene when coming into direct contact with patient bodily waste and fluids. These precautions should be followed for 6 months after BEQVEZ infusion, especially in case of pregnancy or close contact with a person who has a weakened immune system.
- Use of contraception: It is recommended that you and your female partner use appropriate barrier contraception for 1 year after receiving BEQVEZ to prevent DNA to be transferred to a child. For the same reasons, you must not donate semen.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Medicines and herbal supplements which affect the liver and alcohol may impact the response to this medicine and may increase the risk of liver damage.

How BEQVEZ is given:

BEQVEZ will be given to you in a hospital setting under the direction of a healthcare professional experienced and trained in the treatment of Hemophilia B. Your healthcare professional will administer the treatment dose based on your weight. Treatment with BEQVEZ consists of a **one-time single infusion (drip) into a vein**.

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

Usual dose:

Your healthcare professional will determine the correct dose for you based on your body weight. The dose is 5×10^{11} genome copies, the unit BEQVEZ is measured in, per kg of your body weight.

Overdose:

There is no experience of overdose with BEQVEZ.

If you think you, or a person you are caring for, have received too much BEQVEZ, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

BEQVEZ is administered only once.

What are possible side effects from using BEQVEZ?

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

Talk to your healthcare professional if you develop any side effects. These can include:

Very common (may affect more than 1 in 10 people)

- Increased levels of transaminases (liver enzymes) seen in blood tests.
- Headache
- Joint pain
- Respiratory infections

Common (may affect more than 1 in 100 and up to 1 in 10 people)

- Anemia (decreased red blood cells)
- Abdominal (stomach) pain
- Diarrhea
- Dyspepsia (upset stomach)
- Gastrointestinal reflux disease (acid reflux, heartburn)
- Abnormal liver function, fatty liver
- Gastroenteritis (stomach flu)
- Sprain
- Muscle strain
- Coagulation Factor X level decreased
- Back pain
- Joint swelling
- Muscle aches
- Pain in extremity
- Dizziness
- Insomnia
- Cough
- Acne
- High blood pressure

These are not all the possible side effects you may have when taking BEQVEZ. If you experience any side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

BEQVEZ will be stored by the healthcare professionals at your healthcare facility. You will not store BEQVEZ yourself.

If you want more information about BEQVEZ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.pfizer.ca], or by calling 1-800-463-6001 (Pfizer Medical Information).

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