PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ALPROLIX®

Coagulation Factor IX (Recombinant), Fc Fusion Protein

Lyophilized Powder for Solution

250, 500, 1000, 2000, 3000 and 4000 IU/vial

Antihemorrhagic Blood Coagulation Factor IX

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	09/2021
7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	09/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Alprolix (Coagulation Factor IX [Recombinant], Fc Fusion Protein) is indicated in adults and children with hemophilia B (congenital factor IX deficiency or Christmas disease) for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes.
- Control and prevention of bleeding episodes.
- Perioperative management (surgical prophylaxis).

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Alprolix in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics)

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized.

2 CONTRAINDICATIONS

Alprolix is contraindicated in individuals who have manifested severe hypersensitivity reactions, including anaphylaxis, to the product or its components. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For intravenous use only after reconstitution

- Treatment with Alprolix should be initiated under the supervision of a healthcare professional experienced in the treatment of hemophilia B.
- Each vial of Alprolix has the rFIX potency in International Units (IU) stated on the label.
- Dosage and duration of treatment depend on the severity of the factor IX deficiency, the location and extent of bleeding, pharmacokinetic profile, and the patient's clinical condition.
- Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.

4.2 Recommended Dose and Dosage Adjustment

Although dosing can be estimated by the guidelines below, it is recommended that standard routine laboratory tests such as factor IX activity assays be performed (see 7 WARNINGS AND PRECAUTIONS, and 10.3 Pharmacokinetics). Factor IX activity measurements in the clinical laboratory can be affected

by the type of aPTT reagent or reference standard used (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Method of Calculating Initial Estimated Dose:

1 IU of Alprolix per kg body weight is expected to increase the circulating level of factor IX by approximately 1% (IU/dL) in patients ≥12 years of age.

In patients ≥12 years of age, no dose adjustment for recovery is generally required. In pediatric patients <12 years of age, recovery may be lower, and dose should be adjusted accordingly (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

Since patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Alprolix, the expected peak increase in factor IX level expressed as IU/dL (or % of normal) or the required dose can be estimated using the following formulas:

$$\textbf{Dose (IU)} = \textbf{body weight (kg)} \times \textbf{Desired Factor IX Rise (IU/dL or \% of normal)} \times \textbf{Reciprocal of recovery (IU/kg per IU/dL)}$$

OR

$$\textbf{IU/dL (or \% of normal)} = \frac{\textbf{[Total Dose (IU)}}{\textbf{body weight (kg)]}} \times \textbf{Recovery (IU/dL per IU/kg)}$$

Dosing for Routine Prophylaxis:

The recommended starting regimens are either:

50 IU/kg once weekly,

OR

100 IU/kg once every 10-14 days.

Either regimen may be adjusted based on individual response (see 10.3 Pharmacokinetics).

Higher doses or more frequent dosing may be needed in patients <12 years of age.

Dosing for Control and Prevention of Bleeding Episodes:

The following table can be used to guide dosing in bleeding episodes:

Table 1: Bleeding Episode Dosing Guide

Severity of Bleeding	Factor IX Level Required	Dose (IU/kg)/Frequency of Doses (hrs)

	(IU/dL or % of normal)	
Minor and Moderate For example: Joint, superficial muscle/no neurovascular compromise (except iliopsoas), superficial soft tissue, mucous membranes	**30 – 60**	**30 - 60 IU/kg** Repeat every 48 hours if there is further evidence of bleeding
Major For example: Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss; Retroperitoneum, CNS	**80 – 100**	**80 - 100 IU/kg** A repeat dose at 80 IU/kg should be considered after 6-10 hours and then every 24 hours for the first 3 days. Based on the long half-life of Alprolix, the dose may be reduced and frequency of dosing may be extended after Day 3 to every 48 hours.

Adapted from: Roberts and Eberst, WFH 2008, and WFH 2012

Subsequent doses and duration of treatment depends on the individual clinical response, the pharmacokinetic profile, the severity of the factor IX deficiency, and the location and extent of bleeding (see 10.3 Pharmacokinetics).

Higher doses or more frequent dosing may be needed in patients <12 years of age.

Dosing for Perioperative Management (Surgical Prophylaxis)

The following table can be used to guide dosing for perioperative management.

Table 2: Perioperative Management Dosing Guide

Type of Surgery	Initial Factor IX Level Required (IU/dL or % of normal)	Dose (IU/kg)/Frequency of Doses (hrs)
Minor Minor operations including uncomplicated dental extraction	**50 – 80**	**50 - 80 IU/kg** A single infusion may be sufficient. Repeat as needed after 24-48 hours.
Major	**60 - 100 (initial level)**	**100 IU/kg (initial dose)**

Type of Surgery	Initial Factor IX Level Required (IU/dL or % of normal)	Dose (IU/kg)/Frequency of Doses (hrs)
	Days 1 - 3: maintain level 40 - 60% Days 4 - 6: maintain level 30 - 50% Days 7 - 14: maintain level 20 - 40%	A repeat dose at 80 IU/kg should be considered after 6-10 hours and then every 24 hours for the first 3 days. Based on the long half-life of Alprolix, the dose may be reduced and frequency of dosing in the post-surgical setting may be extended after Day 3 to every 48 hours.

Adapted from: Roberts and Eberst, WFH 2008, and WFH 2012

4.4 Administration

Alprolix is administered by intravenous (IV) injection after reconstitution with 0.325% sodium chloride solution.

Detailed instructions for preparation and administration are included in PATIENT MEDICATION INFORMATION**.**

Always wash your hands with soap and water before preparing the product for administration. Check the expiration date of the package. Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

Alprolix should be administered using the infusion set provided with the drug product, and the pre-filled diluent syringe provided.

Reconstitute lyophilized Alprolix powder for injection with the supplied diluent (0.325% sodium chloride solution) from the pre-filled syringe provided. Gently rotate the vial until all of the powder is dissolved.

After reconstitution, the solution is drawn back into the syringe. The solution should be clear to slightly opalescent and colourless.

The injection should be given intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

Dispose of all unused solution, empty vials, and used needles and syringes in an appropriate container and dispose of according to local requirements.

5 OVERDOSAGE

No symptoms of overdose have been reported.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Lyophilized powder nominally containing 250, 500, 1000, 2000, 3000 and 4000 IU/vial. The reconstituted product contains: 50, 100, 200, 400, 600 and 800 IU/mL, respectively.	*For a complete listing see* 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Alprolix (Coagulation Factor IX (Recombinant), Fc Fusion Protein) is formulated as a sterile, preservative-free, non-pyrogenic, lyophilized, white to off-white powder to cake, for intravenous administration in a single use vial.

Each single-use vial contains nominally 250, 500, 1000, 2000, 3000 or 4000 International Units (IU) of Alprolix. Actual Factor IX activity in International Units is stated on the label of each Alprolix vial and carton.

The diluent (Sterile Sodium Chloride Solution, 0.325%) is provided as a liquid in a pre-filled syringe.

When reconstituted with provided diluent, the product contains sucrose, sodium chloride, L-histidine, mannitol, and polysorbate 20.

7 WARNINGS AND PRECAUTIONS

General

The clinical response to Alprolix (may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor IX should be determined, and a sufficient dose of Alprolix should be administered to achieve a satisfactory clinical response. If the patient's plasma factor IX level fails to increase as expected or if bleeding is not controlled after Alprolix administration, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed (see Monitoring and Laboratory Tests).

Carcinogenesis and Mutagenesis

No animal studies investigating carcinogenicity effects of Alprolix have been conducted. Alprolix has not been evaluated in mutagenicity or chromosomal aberration assays.

Hematologic

Thrombotic events with factor IX products have been reported including in patients receiving continuous infusion through a central venous catheter. The safety and efficacy of Alprolix administration by continuous infusion have not been established .. Alprolix should be given intravenously over several minutes. The rate of administration should be determined by the patient's comfort level (see 4 DOSAGE AND ADMINISTRATION4.4 **Error! Reference source not found.**).

Thromboembolic Complications**:**
The use of Factor IX containing products has been associated with the development of thromboembolic complications (e.g., pulmonary embolism, venous thrombosis, and arterial thrombosis). Due to the potential risk for thromboembolic complications, monitor patients on Alprolix for early signs of vascular thrombotic events.

Hepatic/Biliary/Pancreatic

Specific studies of Alprolix in patients with hepatic impairment have not been performed.

Immune

Neutralizing Antibodies (Inhibitors):
Inhibitors have been reported with Alprolix in the treatment of patients with hemophilia B, including in previously untreated patients (PUPs). Patients using Alprolix should be monitored for the development of factor IX inhibitors by appropriate clinical observations and laboratory tests. If the patient's plasma Factor IX level fails to increase as expected or if bleeding is not controlled after Alprolix administration, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed (see Monitoring and Laboratory Tests).

Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with factor IX. Patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. Patients should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of exposure to product

Anaphylaxis and Hypersensitivity Reactions:
Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with Alprolix. Patients experiencing allergic reactions should be evaluated for the presence of inhibitors since they have been associated with allergic reactions with factor IX replacement therapies, including ALPROLIX. Patients with factor IX inhibitors are also at an increased risk of anaphylaxis upon subsequent challenge with factor IX. Advise patients to discontinue use of Alprolix if hypersensitivity symptoms occur and contact a physician and/or seek immediate emergency care.

Monitoring and Laboratory Tests

Monitor plasma factor IX activity levels by performing the one-stage clotting assay to confirm adequate factor IX levels have been achieved and maintained, when clinically indicated. Factor IX results can be affected by the type of aPTT reagent used. Measurement with a one-stage clotting assay utilizing a kaolin-based aPTT reagent will likely result in an underestimation of activity level.

Monitor for the development of factor IX inhibitors. If bleeding is not controlled with Alprolix and the expected factor IX activity plasma levels are not attained, perform an assay to determine if factor IX inhibitors are present (use Bethesda Units to titer inhibitors).

Renal

Alprolix has not been studied in patients with renal impairment.

Nephrotic syndrome has been reported following immune tolerance induction in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX. The safety and efficacy of using Alprolix for immune tolerance induction have not been established.

Reproductive Health: Female and Male Potential

- **Fertility**

Alprolix has not been evaluated in animal fertility studies. It is not known whether Alprolix can affect fertility or sperm development in hemophilia B patients.

- **Function**

No impact on male or female reproductive organs was shown in toxicology studies in rats and monkeys.

7.1 Special Populations

7.1.1 Pregnant Women

Alprolix should be used during pregnancy only if the potential benefit justifies the potential risk. Animal reproductive studies have not been conducted with Alprolix. In a placental transfer study, Alprolix has been shown to cross the placenta in small amounts in mice. Experience regarding the use of factor IX during pregnancy is not available. It is not known whether Alprolix can affect reproductive capacity or cause fetal harm when given to pregnant women.

7.1.2 Breast-feeding

Alprolix should only be administered to nursing mothers if clinically indicated. Lactation studies have not been conducted with Alprolix. It is not known whether Alprolix is excreted into human milk. Caution should be exercised if Alprolix is administered to nursing mothers.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Safety, efficacy and pharmacokinetics of Alprolix have been evaluated in previously treated patients aged between 12 to <18 years old in Study 1 and <12 years old in Study 2. In Study 1, 9 patients received Alprolix as routine prophylaxis and 2 received Alprolix episodically for control of bleeding. The safety of Alprolix, including inhibitor development, have been evaluated in previously untreated pediatric patients (PUPs) less than 18 years of age (median: 0.6 year; range: 0.08-2 years) from Study 4 (see 8 ADVERSE REACTIONS).

No dose adjustment is required for 12 to <18 years of age (see 10.3 Pharmacokinetics and 14 CLINICAL TRIALS). In comparison with adolescents and adults, children <12 years of age may have a lower recovery and higher body weight normalized Factor IX clearance. These differences should be taken into account when dosing. Higher doses or more frequent dosing may be needed in patients <12 years of age (see 10.3 Pharmacokinetics).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of Alprolix did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

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.

Previously treated patients (PTPs)

Alprolix has been evaluated in two open label studies (Study 1 and Study 2) which were conducted in previously treated patients (PTPs) with severe hemophilia B (≤2% endogenous FIX activity). Patients from Study 1 and Study 2 continued to be treated in a long-term extension study (Study 3). A total of 153 subjects have been treated. Thirty (30) (19.6%) were pediatric subjects <12 years of age, 11 (7.2%) were adolescents (12 to <18 years of age), and 112 (73.2%) were adults (≥18 years of age). There were 126 subjects (82.4%) treated for at least 52 weeks, 107 subjects (69.9%) treated for at least 104 weeks and 67 (43.8%) treated for at least 208 weeks. The total number of exposure days (EDs) was 26,106 with a median of 165 (range 1- 528) EDs per subject. Adverse events were monitored for a total of 561 subject-years.

Adverse drug reactions (ADRs) were reported in 14 of 153 (9.2%) subjects treated with Alprolix. Adverse drug reactions are considered adverse events assessed by the investigator as related or possibly related to treatment with Alprolix. Adverse drug reactions in PTPs are summarized in Table 4.

The most common adverse reactions in previously treated patients (PTPs) with an incidence ≥1% for Alprolix were headache, oral paresthesia, and obstructive uropathy.

No subject was withdrawn from the studies due to an adverse drug reaction. In the studies, no inhibitors were detected and no events of anaphylaxis were reported.

Table 4: Adverse Drug Reactions Reported for Alprolix in PTPs in Subjects with at Least One Adverse Event

MedDRA System Organ Class	MedDRA Preferred Term	N=153* Number of Subjects n (%)
Nervous system disorders	Headache Dizziness Dysgeusia	2 (1.3) 1 (0.7) 1 (0.7)
Gastrointestinal disorders	Paresthesia oral Breath odor	2 (1.3) 1 (0.7)
General disorders and administration site conditions	Fatigue Infusion site pain	1 (0.7) 1 (0.7)
Cardiac disorders	Palpitations	1 (0.7)
Renal and urinary disorders	Obstructive uropathy Hematuria Renal colic	2 (1.3) 1 (0.7) 1 (0.7)
Vascular disorders	Hypotension	1 (0.7)
Metabolic and nutrition disorders	Decreased appetite	1 (0.7)

* The Alprolix clinical program included 153 previously treated patients (PTPs) on Alprolix therapy from 2 clinical studies and their extension study (Study 3).

Previously untreated patients (PUPs)

Alprolix safety was also evaluated in one completed study (Study 4) in 33 previously untreated patients (PUPs) with hemophilia B (≤2% endogenous FIX activity). At enrollment, the median age was 0.6 years (range: 0.08-2 years). Overall, the median number of weeks on treatment was 83.01 (range: 6.7-226.7 weeks). The median number of weeks for the episodic treatment regimen was 22.86 (range: 0.3-164.2 weeks), and for the prophylactic treatment regimen was 77.5 (range: 10.1-134.0 weeks). The total number of exposure days (EDs) was 2,233.

The number of patients with at least 10 EDs was 28 (84.8%), at least 20 EDs was 26 (78.8%), and at least 50 EDs) was 21 (63.6%). The median number of EDs was 76 (range: 1-137 days) per subject.

Adverse events were monitored for a total of 57.51 subject-years. Adverse drug reactions (ADRs) were reported in 2 of (6.1%) patients treated with Alprolix. A total of 1 previously untreated patient (3.0%) developed a low-titer factor IX inhibitor that was considered a serious adverse reaction. Adverse drug reactions in PUPs are summarized in Table 5.

Table 5: Adverse Drug Reactions reported for Alprolix in PUPs

MedDRA System Organ Class	MedDRA Preferred Term	N=33 Number of Subjects n (%)
Blood and lymphatic system disorders	Factor IX inhibition*	1 (3.0)
General disorders and administration site conditions	Injection site erythema	1 (3.0)
Immune system disorders	Hypersensitivity*	1 (3.0)

*Both events of factor IX inhibition and hypersensitivity occurred in a single subject while on Alprolix.

8.5 Post-Market Adverse Reactions

During post-marketing experience, the following adverse reactions have been reported:

FIX inhibitor development

Hypersensitivity, including anaphylaxis

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

There are no known drug interactions reported with Alprolix. No drug interaction studies have been performed.

9.5 Drug-Food Interactions

There is no known effect of food on exposure of Alprolix. Therefore, Alprolix may be taken with or without food.

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

Alprolix (Coagulation Factor IX [Recombinant], Fc Fusion Protein) is a long-acting, fully recombinant, fusion protein comprising human coagulation factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1) and produced by recombinant DNA technology.

Factor IX (FIX) is an approximately 55 kDa vitamin K-dependent serine protease, which is an essential clotting factor in the coagulation cascade critical to the hemostasis process. FIX is normally converted

to activated FIX (FIXa) by the activated factor VII/Tissue Factor complex or by activated factor XI. FIXa forms a complex with activated factor VIII on phospholipid surfaces to convert factor X to activated factor X, and which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

Hemophilia B patients have a deficiency of functional FIX, which results in prolonged bleeding after trauma and recurrent spontaneous bleeds into soft tissue and joints. The FIX portion of Alprolix has similar structural and functional characteristics as endogenous FIX and promotes hemostasis by correcting the deficiency of functional FIX.

The other portion of Alprolix is the Fc region of human immunoglobulin G1 (IgG1) which binds with the neonatal Fc receptor (FcRn). This receptor is expressed throughout life by endothelial cells and circulating monocytes and is part of a naturally occurring pathway that is responsible for the long circulating half-life of Fc-containing proteins such as immunoglobulins. These cells internalize serum proteins, and those proteins that do not bind to this recycling receptor proceed to the lysosome and are degraded. In contrast, IgG binds to FcRn in acidic endosomal compartments and is recycled back into circulation, thus extending its serum half-life. Alprolix binds to FcRn thereby utilizing this same naturally occurring pathway to delay lysosomal degradation and allow for longer plasma half-life than endogenous FIX.

Alprolix is used as a replacement therapy to increase plasma levels of factor IX activity, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendency.

10.2 Pharmacodynamics

Hemophilia B is a bleeding disorder characterized by a deficiency of functional clotting factor IX (FIX), which leads to prolonged clotting time in the activated partial thromboplastin time (aPTT) assay, a conventional in vitro test for the biological activity of FIX. Treatment with Alprolix shortens the aPTT over the effective dosing period.

10.3 Pharmacokinetics

The pharmacokinetics of Alprolix compared with BeneFIX® (coagulation Factor IX (recombinant)) were evaluated following a 10-minute IV injection in 22 evaluable subjects (≥19 years) from Study 1. The subjects underwent a washout period of 5 days prior to receiving 50 IU/kg of BeneFIX. Pharmacokinetic sampling was conducted pre-dose followed by assessments at 8 time points up to 96 hours post-dose. Following a washout period of 120 hours (5 days), the subjects received a single dose of 50 IU/kg of Alprolix. Pharmacokinetic samples were collected pre-dose and then subsequently at 11 time points up to 240 hours (10 days) post-dose. A repeat pharmacokinetic evaluation of Alprolix was conducted at Week 26.

Pharmacokinetic parameters were estimated based on the plasma FIX activity over time profile. A central laboratory analyzed all of the PK study plasma samples utilizing a one-stage clotting assay with a silica-based aPTT reagent (Auto APTT, Trinity Biotech) calibrated against factor IX plasma standards. For Alprolix, the maximum activity (C_{max}) was observed immediately following injection, e.g. at 10 minutes from the start of dosing. The geometric mean increase in circulating FIX activity from pre-

injection level was 0.92 IU/dL per IU/kg and the elimination half-life was 82 hours. This half-life is influenced by the Fc region of Alprolix, which in animal models was shown to be mediated by the FcRn cycling pathway. The Alprolix pharmacokinetic profile was stable over repeated dosing as shown by comparable pharmacokinetic parameters at Week 26.

A summary of pharmacokinetic parameters for Alprolix and BeneFIX are presented in Table 6.

Table 6: Summary of Pharmacokinetic Parameters of Alprolix (rFIXFc) and BeneFIX (rFIX)

PK Parameters[1]	Alprolix (95% CI)	BeneFIX (95% CI)	Ratio of Alprolix to BeneFIX (95% CI)
	N=22	N=22	N=22
C_{max} (IU/dL)	40.81 (33.60, 49.58)	43.08 (36.69, 50.59)	0.95 (0.81, 1.11)
AUC/Dose (IU*h/dL per IU/kg)	31.32 (27.88, 35.18)	15.77 (14.02, 17.74)	1.99 (1.82, 2.17)
$t_{1/2\alpha}$ (h)	5.03 (3.20, 7.89)	2.41 (1.62, 3.59)	2.09 (1.18, 3.68)
$t_{1/2\beta}$ (h)	82.12 (71.39, 94.46)	33.77 (29.13, 39.15)	2.43 (2.02, 2.92)
CL (mL/h/kg)	3.19 (2.84, 3.59)	6.34 (5.64, 7.13)	0.50 (0.46, 0.55)
MRT (h)	98.60 (88.16, 110.29)	41.19 (35.98, 47.15)	2.39 (2.12, 2.71)
V_{ss} (mL/kg)	314.8 (277.8, 356.8)	261.1 (222.9, 305.9)	1.21 (1.06, 1.38)
Incremental Recovery (IU/dL per IU/kg)	0.92 (0.77, 1.10)	0.95 (0.81, 1.10)	0.97 (0.84, 1.12)
Time to 1% at 50 IU/kg (days)	11.22 (10.20, 12.35)	5.09 (4.58, 5.65)	2.21 (2.04, 2.39)

[1]PK parameters derived using two compartment model are presented in geometric mean (95% CI)

Abbreviations: CI = confidence interval; C_{max} = maximum activity; AUC = area under the FIX activity time curve; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state

Pediatric Pharmacokinetics (<18 years)

Pharmacokinetic (PK) parameters of Alprolix were determined for adolescents 12 to <18 years of age in Study 1 and for children <12 years of age in Study 2 (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

PK parameters were evaluated following a 10-minute IV infusion in 11 evaluable adolescents who received a single dose of Alprolix. PK samples were collected pre-dose and at multiple time points up to

336 hours (14 days) post-dose. In Study 2, PK parameters were evaluated following a 10-minute IV infusion in 24 evaluable children (<12 years of age) who received a single dose of Alprolix. PK samples were collected pre-dose and at 7 time points up to 168 hours (7 days) post-dose. PK parameters for Alprolix were estimated based on the plasma FIX activity over time profile. A central laboratory analyzed all of the PK study plasma samples utilizing a one-stage clotting assay with a silica-based aPTT reagent (Auto APTT, Trinity Biotech) calibrated against factor IX plasma standards.

Table 7 presents the PK parameters calculated from the pediatric data of 35 subjects <18 years of age. Compared to adults, incremental recovery appeared to be lower and body-weight normalized clearance appeared to be higher in children <12 years of age. This may result in a need for dose adjustments in children <12 years of age (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

Table 7: Comparison of PK Parameters of Alprolix by Age

PK Parameters[1]	Study 2		Study 1
	<6 Years (range: 2, 4)	6 to <12 Years (range: 6, 10)	12 to <18 Years (range: 12, 17)
	N=11	N=13	N=11
IR (IU/dL per IU/kg)	0.5898 (0.5152, 0.6752)	0.7170 (0.6115, 0.8407)	0.8470 (0.6767, 1.0600)
AUC/Dose (IU*h/dL per IU/kg)	22.71 (20.32, 25.38)	28.53 (24.47, 33.27)	29.50 (25.13, 34.63)
$t_{½}$ (h)	66.49 (55.86, 79.14	70.34 (60.95, 81.17)	82.22 (72.30, 93.50)
MRT (h)	83.65 (71.76, 97.51)	82.46 (72.65, 93.60)	93.46 (81.77, 106.81)
CL (mL/h/kg)	4.365 (3.901, 4.885)	3.505 (3.006, 4.087)	3.390 (2.888, 3.979)
V_{SS} (mL/kg)	365.1 (316.2, 421.6)	289.0 (236.7, 352.9)	316.8 (267.4, 375.5)

[1]PK parameters derived from noncompartmental analysis are presented in geometric mean (95% CI)

Abbreviations: CI = confidence interval; IR = incremental recovery; AUC = area under the FIX activity time curve; $t_{1/2}$ = terminal half-life; MRT = mean residence time; CL = clearance; V_{ss} = volume of distribution at steady-state

Special Populations and Conditions

- **Geriatrics:** Clinical studies of Alprolix did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized.
- **Hepatic Insufficiency:** Specific studies of Alprolix in patients with hepatic impairment have not been performed.
- **Renal Insufficiency:** Alprolix has not been studied in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store unopened vials at 2°C to 8°C. The product may be stored at room temperature (15°C to 30°C) for a single 6-month period. The date that the product is removed from refrigeration should be noted on the carton. The product must be used or discarded before the end of this 6-month period. Do not use Alprolix after the expiry date on the label.

Protect from light.

Do not freeze the pre-filled syringe.

Product after reconstitution: The reconstituted product can be stored at room temperature (15°C to 30°C) for 3 hours. Protect from direct sunlight. If it is not used within 3 hours, it must be discarded. The appearance of the reconstituted product should be clear to slightly opalescent and colourless.

12 SPECIAL HANDLING INSTRUCTIONS

Reconstituted Solutions:

Detailed instructions for preparation and administration are included in PATIENT MEDICATION INFORMATION. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

Always wash your hands before performing the following procedures. Aseptic technique should be used during the reconstitution procedure.

Alprolix (Coagulation Factor IX (Recombinant), Fc Fusion Protein) will be administered by intravenous (IV) injection after reconstitution with 0.325% sodium chloride solution (diluent).

Parenteral Products (for reconstitution before use)

Vial Size	Volume of Diluent to be added to vial	Nominal Concentration per mL
250 IU	5 mL	50 IU
500 IU	5 mL	100 IU

Vial Size	Volume of Diluent to be added to vial	Nominal Concentration per mL
1000 IU	5 mL	200 IU
2000 IU	5 mL	400 IU
3000 IU	5 mL	600 IU
4000 IU	5 mL	800 IU

Dispose of all the materials of the packaging in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Coagulation Factor IX (Recombinant), Fc Fusion Protein

Chemical name: Blood coagulation factor IX (synthetic human) fusion protein with immunoglobulin G1 (synthetic human Fc domain fragment), (421->6'), (424 ->9')-bis(disulfide) with immunoglobulin G1 (synthetic human Fc domain fragment)

Molecular formula and molecular mass: The theoretical molecular weight based on the amino acid sequence of rFIXFc, without posttranslational modifications is approximately 98kDa.

Product Characteristics:

rFIXFc is a long-acting, fully recombinant fusion protein consisting of human coagulation factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). The factor IX portion of Coagulation Factor IX (Recombinant), Fc Fusion has a primary amino acid sequence that is identical to the Thr^{148} allelic form of plasma derived factor IX and has structural and functional characteristics similar to endogenous factor IX. The Fc domain of Coagulation Factor IX (Recombinant), Fc Fusion contains the hinge, CH2, CH3 regions of IgG1. Coagulation Factor IX (Recombinant), Fc Fusion contains 867 amino acids with a molecular weight of approximately 98 kilodaltons.

Coagulation Factor IX (Recombinant), Fc Fusion is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized. The cell line expresses Coagulation Factor IX (Recombinant), Fc Fusion into a defined cell culture medium that does not contain any proteins derived from animal or human sources. Coagulation Factor IX (Recombinant), Fc Fusion is purified by a series of chromatography steps that does not require use of a monoclonal antibody. The process includes multiple viral clearance steps including 15 nm virus-retaining nano-filtration. No human or animal additives are used in the cell culture, purification, and formulation processes.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Previously Treated Patients

The safety, tolerability, efficacy and pharmacokinetics of Alprolix were evaluated in 2 multicentre, open-label, prospective studies in previously treated patients (PTPs): a Phase 3 study (Study 1) and a Phase 3 pediatric study (Study 2). Patients from the Study 1 and Study 2 could subsequently enroll in a long-term extension study (Study 3).

Study 1 was designed to assess the efficacy of Alprolix in the treatment of bleeding episodes, in the prevention of bleeding episodes in each of two prophylactic treatment regimens (fixed weekly and individualized interval), as well as in the hemostatic efficacy during perioperative management of

subjects undergoing major surgical procedures. A total of 123 previously treated patients (PTPs) aged 12 to 71 with severe hemophilia B (≤2% endogenous FIX activity) were followed for up to 77 weeks. Subjects were to be assigned to treatment arms according to the standard of care and Investigator decision, following discussion with each subject.

Study 2 was designed to assess the efficacy of Alprolix administered on an individualized prophylactic dose regimen in the treatment and prevention of bleeding episodes. A total of 30 previously treated male pediatric patients with severe hemophilia B (≤ 2% endogenous FIX activity) were enrolled. Subjects were <12 years of age (15 were <6 years of age and 15 were 6 to <12 years of age). All subjects received treatment with Alprolix and were followed for up to 52 weeks.

Study 3 was designed to assess the long-term safety and efficacy of Alprolix for routine prophylaxis, on-demand treatment, and perioperative management. During the study, subjects could change treatment groups. Of the 120 subjects enrolled in Study 3 (aged 3-63), 93 were from Study 1 and 27 were from Study 2.

From the start of Study 1 to the end of Study 3, patients received a median of 189 (1-338) weeks of treatment. From the start of Study 2 to the end of Study 3, subjects received a median of 150 (17-251) weeks of treatment.

Table 8: Summary of study design and patient demographics

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Median age (Range)**			**Gender**
Study 1	Open-label, multicentre	Arm 1: Individualized dose (IV) every 7 days	63	28 (12, 71)			Male
		Arm 2: 100 IU/kg (IV) at individualized intervals	29	33 (12, 62)			
		Arm 3: As needed for treatment of bleeding episodes	27	36 (14, 64)			
		Arm 4: As needed for maintaining hemostasis during surgery	12	34.5 (17, 61)			
Study 2	Open-label, multicentre	Individualized prophylaxis (starting regimen of 50 to 60 IU/kg every 7 days); IV	30	5.0 (1, 11)			Male
			Total (n=120)	**Study 1 (n=93)**	**Study 2 (<6 y) (n=13)**	**Study 2 (6 to <12 y) (n=14)**	

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Median age (Range)			Gender
Study 3*	Open-label, multicentre	Individualized prophylaxis (IV) every 7 days	74	n=51 29.0 (13,62)	n=13 3.0 (3,5)	n=10 9.0 (7,10)	Male
		Individualized prophylaxis (IV)	36	n=31 34.0 (13,63)	0	n=5 11.0 (9,12)	
		Personalized prophylaxis	19	n=17 33.0 (19,63)	n=1 4.0 (4,4)	n=1 12.0 (12,12)	
		Episodic treatment	15	n=15 25.0 (20,60)	0	0	

* Subjects were permitted to change treatment regimens over the course of the extension study; therefore, individual subjects may be represented in more than one treatment regimen group.

Study 1 (≥12 Years)

In the clinical study, 121 subjects were followed for a median duration of 51.4 weeks (range <1-77). Of the 114 subjects assessed for efficacy, 87 received prophylaxis (fixed weekly interval (n=61) or individualized interval (n=26)) and 27 received episodic treatment. The observed median annualized bleeding rate (ABR) was 2.95 for subjects in the fixed weekly interval prophylactic regimen arm, and 1.38 for subjects in the individualized interval prophylactic arm (Table 9).

Table 9: Annualized Bleed Rate (ABR) by Prophylaxis Arm in Subjects ≥12 Years of Age

	Prophylaxis Fixed Weekly Interval (N=61)	Prophylaxis Individualized Interval (N=26)
Median Overall ABR (range)	2.95 (0.0, 12.8)	1.38 (0.0, 8.9)
Median Spontaneous ABR (range)	1.04 (0.0, 10.8)	0.88 (0.0, 6.2)
Median Traumatic ABR (range)	0.99 (0.0, 5.2)	0.00 (0.0, 8.4)
Joint ABR (range)	1.11 (0.0, 12.8)	0.36 (0.0, 7.8)

A comparison of the estimated number of bleeding episodes per subject in the 12 months prior to study start, which was based on data provided by the investigator and derived from source documentation in the subject's medical records, to the estimated annualized number of on study bleeding episodes per subject for subjects on a prior prophylaxis regimen is shown in Table 10.

Table 10: Estimated Number of Bleeding Episodes per Subject in the Prior 12 Months as Compared to the Estimated Annualized Number of Bleeding Episodes per Subject On-study in Subjects ≥12 Years of Age

	Prophylaxis (Arm 1) Fixed Weekly Interval	Prophylaxis (Arm 2) Individualized Interval
Number of subjects on prophylactic regimen prior study	29	10
Negative binomial model estimated annualized number of bleeding episodes per subject (95% CI)		
Prior 12 months	4.81 (3.07, 7.52)	2.48 (1.42, 4.34)
On-study	2.56 (1.84, 3.56)	1.51 (0.56, 4.06)

9 out of 48 subjects who were on prophylactic treatment regimen prior to study were excluded from the analysis: 3 subjects did not have sufficient data to be included in the efficacy analysis, 4 subjects had missing pre-study estimated number of bleeding episodes in 12 months and 2 subjects were on sports prophylaxis rather than a routine prophylaxis regimen.

Study 2 (<12 Years)

Thirty (30) subjects received Alprolix on an individualized prophylactic dose regimen. The median duration of treatment on study was 49.4 weeks (range 12 to 52). The observed median annualized bleeding rate (ABR) was 1.09 for subjects <6 years of age, 2.13 for subjects 6 to <12 years of age and 1.97 for the overall group of <12 years of age Table 11.

Table 11: Annualized Bleed Rate (ABR) in Pediatric Subjects <12 Years of Age

	<6 Years (N=15)	6 to <12 Years (N=15)	Total (<12 Years) (N=30)
Median Overall ABR (range)	1.09 (0.0, 5.6)	2.13 (0.0, 10.)	1.97 (0.0, 10.0)
Median Spontaneous ABR (range)	0.00 (0.0, 2.9)	0.00 (0.0, 3.1)	0.00 (0.0, 3.1)
Median Traumatic ABR (range)	0.00 (0.0, 5.6)	1.06 (0.0, 9.6)	0.53 (0.0, 9.6)
Median Joint ABR (range)	0.00 (0.0, 2.3)	1.06 (0.0, 8.7)	0.00 (0.0, 8.7)

A comparison of the estimated number of bleeding episodes per subject in the 12 months prior to study start, which was based on data provided by the investigator and derived from source documentation in the subject's medical records, to the estimated annualized number of on study bleeding episodes per subject for subjects on a prior prophylaxis regimen is shown in Table 12.

Table 12: Estimated Number of Bleeding Episodes per Subject in the Prior 12 Months as Compared to the Estimated Annualized Number of Bleeding Episodes per Subject On-study in Pediatric Subjects <12 Years of Age

	<6 Years	6 to <12 Years	Total
Number of subjects on prophylactic regimen prior to study	15	15	30
Negative binomial model estimated annualized number of bleeding episodes per subject (95% CI)			
Prior 12 months	3.88 (2.19, 6.87)	7.20 (2.10, 24.66)	5.54 (2.41, 12.72)
On-study	1.80 (1.05, 3.10)	2.80 (1.6.1, 4.85)	2.31 (1.54, 3.47)

Study 3 (extension study)

The results from Study 3 for routine prophylaxis were consistent with those of Study 1 and Study 2.

Efficacy in Control of Bleeding:

Study 1 (≥12 Years)

A total of 636 bleeding events were observed in the fixed dose, fixed interval, and the episodic (on-demand) arms. The number of injections to treat bleeding episodes and the dose are summarized in Table 13.

Table 13: Summary of Bleeding Episodes and Dose of Alprolix in Arms 1, 2 and 3 Combined in Subjects ≥12 Years of Age

Bleeding Episodes	N=636
# of injections to treat bleeding episodes	
1 injection	575 (90.4%)
2 injections	44 (6.9%)
3 injections	17 (2.7%)
Median average dose per injection (IU/kg) to treat a bleeding episode (range)	46.07 (7.9, 111.1)
Median total dose (IU/kg) to treat a bleeding episode (range)	46.99 (7.9, 263.9)

In the episodic (on-demand) arm, the observed median annualized bleed rate was 17.69. The median spontaneous annualized bleed rate was 11.78 and the median traumatic annualized bleed rate was 2.21.

The response to each injection for a bleeding episode was evaluated and recorded by subjects at 8 to 12 hours post-treatment. Responses were recorded using a 4-point scale: excellent, good, moderate, and no response. A total of 714 injections were administered for 636 bleeding episodes; 690 out of 714 injections were evaluated (Table 14).

Table 14: Subject's Assessment of Response to Alprolix Injections by Type of Bleeds and Location of Bleeds (Arms 1, 2 and 3 Combined) in Subjects ≥12 Years of Age

Type / Location of Bleeds	**Number of Injections**	**Excellent**	**Good**	**Moderate**	**No response**
Spontaneous bleeding episodes	438	168 (38.4%)	197 (45.0%)	65 (14.8%)	8 (1.8%)
Traumatic bleeding episodes	218	61 (28.0%)	116 (53.2%)	35 (16.1%)	6 (2.8%)
Unknown Type bleeding episodes	34	9 (26.5%)	15 (44.1%)	10 (29.4%)	0 (0.0%)
Joint bleeds	526	193 (36.7%)	237 (45.1%)	85 (16.2%)	11 (2.1%)
Muscle bleeds	152	39 (25.7%)	94 (61.8%)	18 (11.8%)	1 (0.7%)
Internal bleeds	33	7 (21.2%)	9 (27.3%)	14 (42.4%)	3 (9.1%)
Skin bleeds	38	14 (36.8%)	16 (42.1%)	7 (18.4%)	1 (2.6%)

Study 2 (<12 Years)

A total of 60 bleeding events were observed during the study. The number of injections to treat bleeding episodes and the dose are summarized in Table 15.

Table 15: Summary of Bleeding Episodes and Dose of Alprolix to Treat a Bleeding Episode in Pediatric Subjects <12 Years of Age

	<6 Years N=15	**6 to <12 Years N=15**	**Total (<12 Years) N=30**
Bleeding episodes	N=22	N=38	N=60
# of injections to treat bleeding episodes			
1 injection	19 (86.4%)	26 (68.4%)	45 (75.0%)
2 injections	2 (9.1%)	8 (21.1%)	10 (16.7%)
3 injections	1 (4.5%)	4 (10.5%)	5 (8.3%)

For subjects <12 years of age, the median average dose per injection to treat a bleeding episode was 63.51 IU/kg (range: 16.7, 133.3) and the median total dose to treat a bleeding episode was 68.22 (range: 16.7, 362.7).

Assessment of response to each injection was recorded by subjects at 8 to 12 hours post treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. A total of 80 injections have been administered for 60 bleeding episodes; 67 of these injections were evaluated for response (Table 16).

Table 16: Subject's Assessment of Response to Alprolix Injections by Type of Bleeds and Location of Bleeds in Subjects <12 Years of Age

Type/ Location of Bleeds	Number of Injections Evaluated n			Excellent n (%)			Good n (%)			Moderate n (%)			No Response n (%)		
	<6 Years	6 to <12 Years	Total	<6 Years	6 to <12 Years	Total	<6 Years	6 to <12 Years	Total	<6 Years	6 to <12 Years	Total	<6 Years	6 to <12 Years	Total
Spontaneous bleeding episodes	6	10	16	4 (66.7)	5 (50.0)	9 (56.3)	2 (33.3)	4 (40.0)	6 (37.5)	0 (0.0)	1 (10.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Traumatic bleeding episodes	16	35	51	6 (37.5)	14 (40.4)	20 (39.2)	8 (50.0)	17 (48.6)	25 (49.0)	1 (6.3)	4 (11.4)	5 (9.8)	1 (6.3)	0 (0.0)	1 (2.0)
Unknown Type bleeding episodes	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint bleeds	4	29	33	1 (25.0)	15 (51.7)	16 (48.5)	3 (75.0)	10 (34.5)	13 (39.4)	0 (0.0)	4 (13.8)	4 (12.1)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle bleeds	5	11	16	1 (20.0)	2 (18.2)	3 (18.8)	3 (60.0)	8 (72.7)	11 (68.8)	1 (20.0)	1 (9.1)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Internal bleeds	4	2	6	3 (75.0)	1 (50.0)	4 (66.7)	0 (0.0)	1 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)
Skin/mucosa bleeds	12	3	15	8 (66.7)	1 (33.3)	9 (60.0)	4 (33.3)	2 (66.7)	6 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Study 3 (extension study)

The results from Study 3 for control of bleeding were consistent with those of Study 1 and Study 2.

Efficacy in Perioperative Management (Surgical Prophylaxis):

Major Surgeries

There were a total of 35 major surgeries in 22 subjects in Study 1 and Study 3. Of the 35 major surgeries, 28 surgeries (80.0%) required a single dose to maintain hemostasis during surgery. The median average dose per injection to maintain hemostasis during surgery was 94.7 IU/kg (range: 49 to 152 IU/kg).

Hemostasis was assessed post-operatively by the investigator using a 4-point scale of excellent, good, fair, and none. The hemostatic response was assessed for 33 major surgeries and 100% were rated as excellent or good. There was no clinical evidence of thrombotic complications in any of the subjects.

Hemostatic response to dosing during surgery and post-operatively for Study 1 and Study 3 is summarized in Table 17.

Table 17: Summary of Hemostatic Response during Surgery and Post-Operatively

Major Surgery	# of Procedures (# of Subjects)	Response	
		Excellent	Good
Ablation of Liver Lesion	1 (1)	1	
Arthroscopy	2 (2)	2	
Closure of Rectal Fistula	1 (1)	1	
Craniotomy	1 (1)	1	
Dental Abscess	1 (1)	1	
Finger Amputation or Partial Amputation	2 (1)	2	
Hip Replacement or Repair	2 (2)	1	1
Install or Remove External Ilizarov Fixator	2 (1)	2	
Liver Resection	1 (1)	1	
Liver Transplant	1 (1)	1	
Orchiectomy	1 (1)	1	
Patellar Resurfacing	1 (1)	1	
Pilonidal Cyst	1 (1)	1	
Pin Release	1 (1)	1	
Spinal Surgery	2(2)	1	1
Tendon Transfer in Right Arm	1 (1)	1	
Tonsillectomy	1 (1)	1	
Unilateral Ankle Fusion	2 (2)	2	
Unilateral Ankle Replacement or Revision	1 (1)	1	
Unilateral Knee Replacement or Revision	8(8)	6	2

[1]Two surgeries were not assessed for response

Minor Surgeries

A hemostatic assessment in 62 minor surgical procedures in 37 subjects was conducted in Study 1, Study 2, and Study 3. Hemostatic response was assessed for 38 minor surgeries; 36 minor surgeries were rated as excellent or good and 2 as fair.

Impact on Quality of Life:
In Study 1, Quality of Life was measured using the HAEM-A-QOL, a quality of life instrument specific to hemophilia. HAEM-A-QOL was performed in a subset of adult subjects (aged 18 and older) in the prophylactic treatment arms. Lower scores represent better quality of life; therefore, a negative change from baseline represents improvement during the course of the study. Change from baseline at Week 26 in the combined prophylaxis arms by pre-study regimen are summarized in Table 18.

Table 18: Median Change from Baseline for the Haem-A-QOL Questionnaire (Fixed Weekly Interval and Individualized Interval Arms Pooled)

	Pre-Study Regimen					
	Prophylaxis			**Episodic (On-demand)**		
	N	**Change from baseline**		**N**	**Change from baseline**	
Total Score	27	-6.82	(-22.8, 6.1)	26	-6.25	(-25.5, 12.8)
Domains, during the past month						
1. Physical Health	27	-10.00	(-45.0, 20.0)	31	-15.00	(-60.0, 15.0)
2. Feeling	27	0.00	(-43.8, 50.0)	31	0.00	(-43.8, 62.5)
3. View of Yourself	27	-5.00	(-25.0, 15.0)	30	-5.00	(-35.0, 25.0)
4. Sports and leisure	22	-7.50	(-70.0, 25.0)	21	-20.00	(-40.0, 35.0)
5. Work and school	22	0.00	(-31.3, 52.1)	25	-6.25	(-31.3, 18.8)
6. Dealing with hemophilia	27	0.00	(-100.0, 100.0)	31	-8.33	(-66.7, 75.0)
7. Treatment	27	-6.25	(-18.8, 18.8)	31	0.00	(-53.1, 37.5)
Domains, recently						
8. Future	26	-5.00	(-25.0, 10.0)	30	0.00	(-30.0, 20.0)
9. Family Planning	15	0.00	(-29.2, 12.5)	13	0.00	(-43.8, 25.0)
10. Partnership and sexuality	26	0.00	(-50.0, 66.7)	30	0.00	(-25.0, 25.0)

NOTE: summary statistics are median (minimum, maximum)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Results of repeat-dose studies in two animal species, rats and monkeys, using IV administration, revealed no safety findings relevant to use in humans. Rats were dosed for 4 weeks while monkeys were dosed for 5 and 27 weeks in 2 separate studies. The highest dose, 1000 IU/kg, provides a safety margin of 20-fold relative to a starting dose of 50 IU/kg for patients and a 10-fold relative to a starting dose of 100 IU/kg for patients. There were no concerns for local tolerance or thrombogenic potential based on rabbit studies.

Table 19: Summary of Toxicology Studies

Study Number and Title	Species	Dose and Frequency	Key Findings
Repeat-Dose Toxicology Studies			
4-Week IV Dose Toxicity and PK Study of FIXFc in Rats Followed by a 4-Week Recovery Period	Sprague-Dawley Rats	0, 50, 200 and 1000 IU/kg Every 4 days for 4 weeks (8 IV doses)	Repeat doses were well-tolerated Antibodies to rFIXFc (≈50% at 50 and 200 IU/kg and ≈75% at 1000 IU/kg) NOAEL was 1000 IU/kg
5-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-week Recovery Period	Cynomolgus Monkeys	0, 50, 200 and 1000 IU/kg Once weekly IV for 5 weeks	Repeat doses were well-tolerated Dose-related increases in Antibodies to rFIXFc Transient increases in PT, primarily at 1000 IU/kg (artifact of in vitro assay conditions) NOAEL was 1000 IU/kg Transient increases in PT were an artifact due to high plasma concentrations of rFIXFc which interfered with in vitro assay conditions used to measure PT.
27-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	Cynomolgus Monkeys	0, 50, 200 and 1000 IU/kg Once weekly IV for 27 weeks	Repeat doses were well-tolerated Hypersensitivity (2 of 12 high dose animals) Antibodies to rFIXFc (18 of 28 treated animals); no neutralization of endogenous FIX NOAEL was 1000 IU/kg

Study Number and Title	Species	Dose and Frequency	Key Findings
Local Tolerance Study			
Single Dose IV and Paravenous Local Tolerance Study of Lyophilized rFIXFc in New Zealand White Rabbits	New Zealand White Rabbits	Formulation 1: 198 IU/kg Formulation 2: 110 IU/kg Single dose (IV and PV)	Single administration (IV or PV) of rFIXFc was well-tolerated There were no local injection site reactions attributed to either lot of rFIXFc
Thrombogenicity Studies			
Evaluation of the Thrombogenic Potential of FIXFc Using the Wessler Stasis Model in New Zealand White Rabbits	New Zealand White Rabbits	50, 200, 987 IU/kg Single dose (IV)	No enhancement of thrombus formation compared to saline or BeneFIX
Evaluation of Thrombogenic Potential of FIXFc Phase 3a DP Using the Wessler Stasis Model in New Zealand White Rabbits	New Zealand White Rabbits	50, 200, 1000 IU/kg Single dose (IV)	No enhancement of thrombus formation compared to saline and vehicle Reduced thrombus formation compared to BeneFIX

IV = intravenous; PT = prothrombin time; PV = paravenous

Teratogenicity: Alprolix has not been evaluated in animal reproductive studies. In a placental transfer study, Alprolix has been shown to cross the placenta in small amounts in mice.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ALPROLIX® [pronounced all' prō liks]

Coagulation Factor IX (Recombinant), Fc Fusion Protein

Read this carefully before you start taking **Alprolix** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Alprolix.**

What is Alprolix used for?

- Alprolix is used to help control and prevent bleeding in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease.

How does Alprolix work?

Alprolix is coagulation Factor IX made in the laboratory using recombinant technology. It can be used to help people with Hemophilia B who do not have enough natural coagulation factor IX in their blood to form clots.

What are the ingredients in Alprolix?

Medicinal ingredients: Coagulation Factor IX (Recombinant), Fc Fusion Protein

Non-medicinal ingredients: L-histidine, mannitol, polysorbate 20, sodium chloride and sucrose

Alprolix comes in the following dosage forms:

Powder in a vial.
Available nominally in 250, 500, 1000, 2000, 3000 and 4000 IU/vial.

Before use, the powder in the vial must be mixed with the liquid in the pre-filled syringe. After mixing, the actual activity level is printed in International Units on the label. The product contains approximately 50, 100, 200, 400, 600 and 800 IU/mL

Do not use Alprolix if:

- Have an allergy or are sensitive to Alprolix or any ingredients listed below.

If you are not sure if you should use Alprolix, talk to your doctor.

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

- Are pregnant or planning to become pregnant. It is not known if Alprolix may harm your unborn baby.
- Are breastfeeding. It is not known if Alprolix passes into the milk and if it can harm your baby.
- Have any allergies to this drug or its ingredients or components of the container (see When it should not be used).

Allergic reactions may occur with Alprolix. Call your doctor or get emergency treatment right away if you have any of the following symptoms:

- Difficulty breathing
- Chest tightness
- Swelling of the face
- Rash
- Hives

Alprolix may increase the risk of formation of abnormal blood clots in your body if you have risk factors for developing blood clots.

Your body can also make antibodies called "inhibitors" against Alprolix, which may stop Alprolix from working properly

Other warnings you should know about:

Allergic reactions may occur with Alprolix (see 7 WARNINGS AND PRECAUTIONS).

Some common side effects of Alprolix are headache, abnormal sensation in the mouth and obstructive uropathy (pain in your side with blood in your urine).

Alprolix may increase the risk of formation of abnormal blood clots in your body if you have risk factors for developing blood clots.

Your body can also make antibodies called 'inhibitors' against Alprolix. These inhibitors may stop Alprolix from working properly. Tell your doctor if you are using increasing amounts of Alprolix to control or prevent bleeding.

Talk to your doctor about any side effect that bothers you or that does not go away.

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

The following may interact with Alprolix:

- other prescription or non-prescription medicines. This includes vitamin or mineral supplements, herbal products or natural health products.

How to take Alprolix:

Always follow your doctor's instructions for taking Alprolix. The first time you inject Alprolix, you should be under proper medical supervision, where proper medical care for severe allergic reactions could be provided.

Read all the instructions before you start. There are 5 steps, explained in this guide.

A. Setting Up
B. Reconstituting the injection
C. Pooling
D. Giving the injection
E. Post-Injection Care and Disposal

A. Setting Up

Ensure that your work area is clean.
Collect everything you will need. Wash your hands thoroughly with soap and water before performing the following procedures.

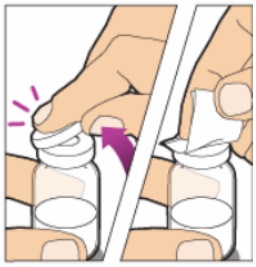
Check the expiry date on the Alprolix package. If it is out of date, do not use it and contact your clinic immediately. Obtain a replacement package. If refrigerated, allow the vial of Alprolix and pre-filled diluent syringe to reach room temperature before use.

Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

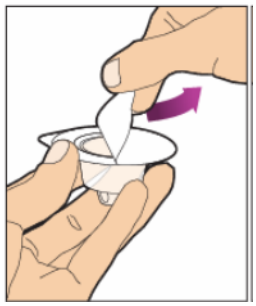
Use the diluent in the pre-filled syringe supplied in the package.

Actual factor IX activity in International Units is stated on the label of each Alprolix carton and vial.

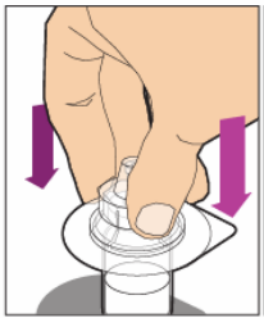
Remove the plastic cap from the Alprolix vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.



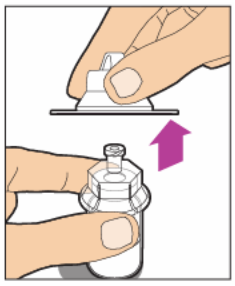
Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the package of the adapter.



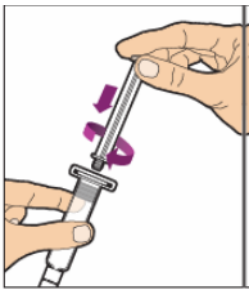
Keep the vial on a flat surface. Hold the vial adapter package with one hand and using the other hand, place the vial adapter over the vial. Place the adapter spike directly above the centre of the rubber stopper. Push the vial adapter straight down until the adapter spike punctures the centre of the vial stopper and is fully inserted.



Lift the package cover away from the vial adapter and discard the cover.

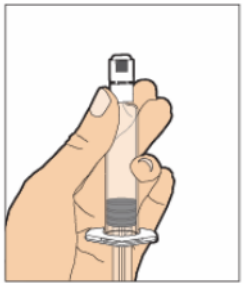


Take the plunger rod and syringe out of the package. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn clockwise until it is securely attached. Only use the diluent syringe provided in the Alprolix package.

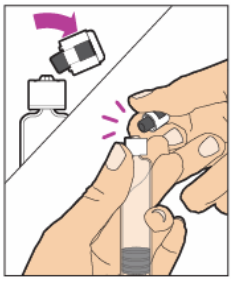


B. Reconstituting the injection

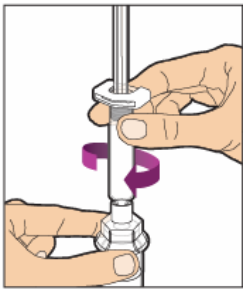
With one hand, hold the diluent syringe by the ridged part right under the cap, with the cap pointing up. Do not use if the cap has been removed or is not securely attached.



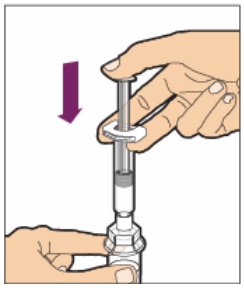
With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe or inside of the cap.



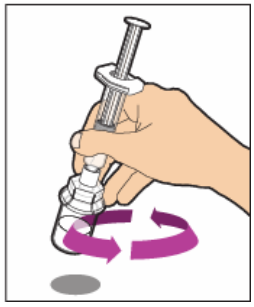
Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe clockwise until it is securely attached to the adapter.



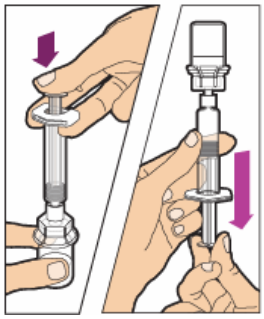
Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.



With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. The final solution should be clear to slightly opalescent and colourless. Do not shake. Do not use the reconstituted Alprolix if it contains visible particles or is cloudy.

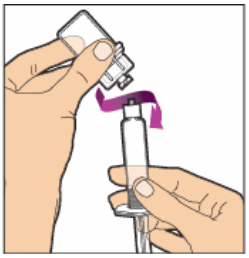


Make sure the plunger rod is completely depressed. Turn the vial upside-down. Slowly pull on the plunger rod to draw the solution into the syringe. Be careful not to pull the plunger rod completely out of the syringe.



Gently unscrew the syringe from the vial adapter and dispose of the vial with the adapter still attached. Do not touch the syringe tip or the inside of the cap.

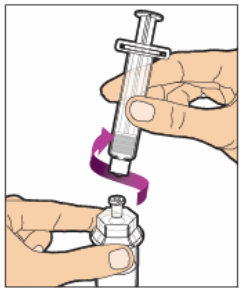
Your Alprolix is now ready to be connected to your infusion tubing set. See section D. Use the reconstituted Alprolix as soon as possible, but no later than 3 hours after reconstitution. Protect from direct sunlight. **Do not refrigerate after reconstitution.**



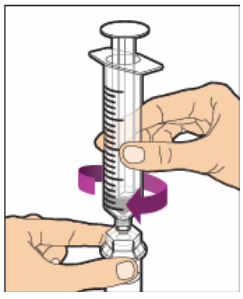
C. Pooling

If you are using two or more vials of Alprolix, you can follow these pooling steps. Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a large luer lock syringe. Do not detach the diluent syringe or the large luer syringe until you are ready to attach the large luer lock syringe to the next vial (with vial adapter attached).

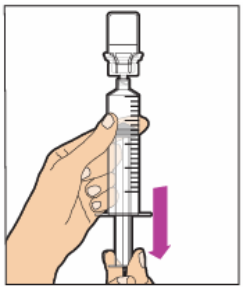
Remove the diluent syringe from the vial adapter by turning it counterclockwise until it is completely detached.



Attach a separate large luer lock syringe by turning clockwise until it is securely attached.



Slowly pull on the plunger rod to draw the solution into the syringe. Repeat this pooling procedure with each vial you will be using. Once you have pooled the required dose, proceed to administration using the large luer lock syringe.

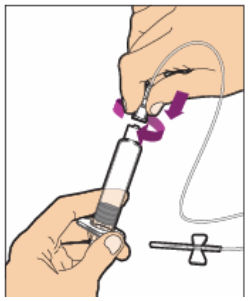


D. Giving the injection
For Intravenous Injection only after Reconstitution

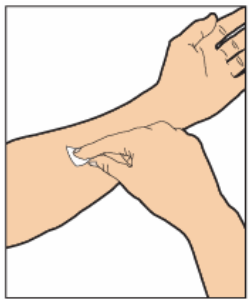
Inspect the reconstituted Alprolix solution visually for particulate matter and discolouration prior to administration. Do not use if particulate matter or discolouration is observed.

Do not administer reconstituted Alprolix in the same tubing or container with other medications.

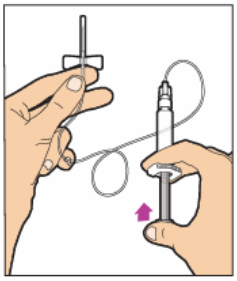
Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. Do not remove the protective needle cover until you are ready to insert the needle.



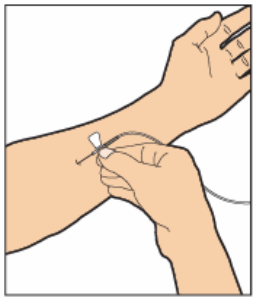
Apply a tourniquet and clean the skin area where you will perform the injection using an alcohol wipe.



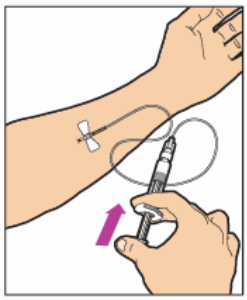
Depress the plunger until all air is removed from the syringe and Alprolix has reached the end of the infusion set tubing. Do not push Alprolix through the needle.



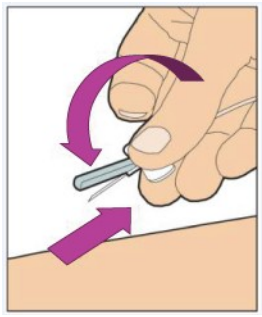
Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



Slowly depress the plunger on the syringe to administer Alprolix. Alprolix should be injected intravenously over several minutes. The rate of administration should be determined by your comfort level. The small amount of drug product left in the infusion set will not affect treatment.

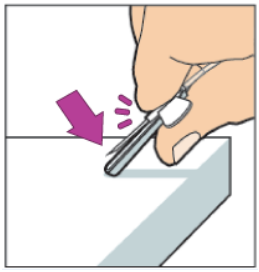


After infusing Alprolix, flip the safety shield towards the needle. Remove the infusion set.

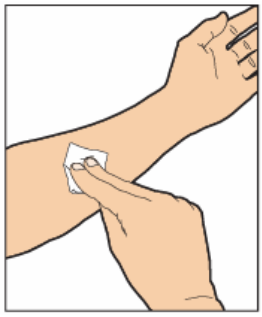


Post-Injection Care and Disposal

Place the wing and the safety shield between your thumb and index finger. Press the safety shield against a hard surface until an audible click is heard.



Use a sterile gauze to put pressure on the infusion site for several minutes. Apply an adhesive bandage if necessary.



A sharps bin should be used for disposal of all unused solution, empty vials and used needles and syringes.

Usual dose:
Your doctor will prescribe the dose you should take. The steps in Preparing Your Dose for Administration are general guidelines for using Alprolix. If you are unsure of these procedures, please call your healthcare provider before using.

Overdose:

No symptoms of overdose have been reported.

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

Missed Dose:

Use your dose of Alprolix as soon as you remember and then resume your normal dosing schedule.

Do not use a double dose to make up for the dose that you missed.

If you are not sure what to do, ask your doctor or pharmacist.

What are possible side effects from using Alprolix?

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
The following side effects could mean you are having an allergic reaction.			
Difficult breathing			√
Chest tightness			√
Swelling of the face, rash or hives			√

If you have a troublesome symptom or 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:

Keep the vials of Alprolix in the refrigerator at 2°C to 8°C.

You can keep the vials of Alprolix at room temperature at 15°C to 30°C for a single 6-month period.

Write the date that you take the product out of the refrigerator on the carton to help you remember. You must either use the product or dispose of it before the end of this 6-month period.

Do not freeze the product otherwise the pre-filled diluent syringe may be damaged.

Protect the Alprolix vials from light.

After reconstitution, you can keep the product at room temperature at 15°C to 30°C for three (3) hours. Protect from direct sunlight. If you do not use the product within 3 hours, you must not use it. Do not use Alprolix if the reconstituted solution is not clear to slightly opalescent and colourless.

Throw away any unused Alprolix.

Do not use product or diluent after the expiry date that is shown on the label of the vial and the carton.

If you want more information about Alprolix:

- 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.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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