NEW ZEALAND DATA SHEET

1 ALPROLIX (POWDER FOR INFUSION)

ALPROLIX 250 International Units (IU), Powder for infusion
ALPROLIX 500 IU, Powder for infusion
ALPROLIX 1000 IU, Powder for infusion
ALPROLIX, 2000 IU, Powder for infusion
ALPROLIX, 3000 IU, Powder for infusion
ALPROLIX, 4000 IU, Powder for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alprolix 250 IU: Each single-use vial contains nominally 250 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 50 IU of eftrenonacog alfa (rhu[1]).

Alprolix 500 IU: Each single-use vial contains nominally 500 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 100 IU of eftrenonacog alfa (rhu[1]).

Alprolix 1000 IU: Each single-use vial contains nominally 1000 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 200 IU of eftrenonacog alfa (rhu[1]).

Alprolix 2000 IU: Each single-use vial contains nominally 2000 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 400 IU of eftrenonacog alfa (rhu[1]).

Alprolix 3000 IU: Each single-use vial contains nominally 3000 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 600 IU of eftrenonacog alfa (rhu[1]).

Alprolix 4000 IU: Each single-use vial contains nominally 4000 IU of eftrenonacog alfa (rhu). After reconstitution, each mL of solution for injection contains 800 IU of eftrenonacog alfa (rhu[1]).

For the full list of excipients, see *Section 6.1 LIST OF EXCIPIENTS*.

3 PHARMACEUTICAL FORM

Powder for infusion

[1] rhu: Produced in human embryonic kidney (HEK) 293H cells by recombinant DNA technology.

ALPROLIX is formulated as a sterile, preservative-free, non-pyrogenic, lyophilised, white to off-white powder to cake, for intravenous (IV) administration in a single-use vial. The liquid diluent is in a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ALPROLIX is a long-acting anti-haemophilic factor (recombinant) indicated in adults and children with haemophilia B (congenital factor IX deficiency) for:

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

4.2 Dose and Method of Administration

For Intravenous Use Only After Reconstitution.

Treatment should be initiated and supervised by qualified healthcare professionals experienced in the diagnosis and treatment of haemophilia B. The ability of a patient to self-inject intravenously should be assessed.

Each vial of ALPROLIX has the recombinant FIX potency in International Units stated on the label.

Careful control of replacement therapy is especially important in cases of life-threatening bleeding episodes or major surgery *(*see Table 1 and Table 2*).*

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).*

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 or older.

ALPROLIX has been shown to have a prolonged circulating half-life. In patients 12 years of age or older, no dose adjustment for recovery is generally required. In paediatric patients less than 12 years of age, recovery may be lower and dose should be adjusted accordingly (*see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use)*. Since patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses to ALPROLIX, the expected *in vivo* peak increase in factor IX level expressed as IU/dL (or % of normal) or the required dose can be estimated using the following formulae:

IU/dL (or % of normal) = [Total Dose (IU)/body weight (kg)] x recovery (IU/dL per IU/kg)

OR

Dose (IU) = body weight (kg) x Desired Factor IX Rise (IU/dL or % of normal) x reciprocal of recovery (IU/kg per IU/dL)

Control and Prevention of Bleeding Episodes

Table 1 can be used to guide dosing in bleeding episodes:

Table 1: Guide to ALPROLIX Dosing for Treatment of Bleeding

Severity of Bleed	Factor IX Level Required (IU/dL or % of normal)	Dose (IU/kg)/ Frequency of Doses (hrs)
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**	**100 IU/kg** For repeat dosing, follow guidelines for major surgery (see Table 2)

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

Subsequent dosage and duration of treatment depends on the individual clinical response, pharmacokinetic profile, the severity of the factor IX deficiency, and the location and extent of bleeding.

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

Perioperative Management

Table 2 can be used to guide dosing for perioperative management (surgical prophylaxis):

Table 2: Guide to ALPROLIX Dosing for Perioperative Management (Surgical Prophylaxis)

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 to 80**	**50-80 IU/kg** A single infusion may be sufficient. Repeat as needed after 24-48 hours.
Major	**60 to 100 (initial level)** Days 1-3: maintain level 40-60% Days 4-6: maintain level 30-50% Days 7-14: maintain level 20-40%	**100 IU/kg (initial dose)** 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

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

Routine Prophylaxis
The recommended starting regimens are either:

50 IU/kg once weekly or 100 IU/kg once every 10 days.

Either regimen may be adjusted based on patient response *(see Section 5.2 PHARMACOKINETIC PROPERTIES).*

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

4.3 Contraindications

ALPROLIX is contraindicated in patients who have manifested severe hypersensitivity reactions, including anaphylaxis, to the product or its components (excipients listed in *Section 6.1 LIST OF EXCIPIENTS*).

4.4 Special Warnings and Precautions for Use

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 (neutralising antibodies) should be suspected, and appropriate testing performed *(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Monitoring Laboratory Tests)*.

Anaphylaxis and Hypersensitivity Reactions
Allergic type hypersensitivity reactions, including anaphylaxis, are possible with factor replacement therapies, and have been reported with ALPROLIX. The presence of inhibitors has been associated with allergic reactions with factor IX replacement therapies, including with ALPROLIX. Advise patients to discontinue use of ALPROLIX if hypersensitivity symptoms occur and contact a physician and/or seek immediate emergency care.

Thromboembolic Complications
Thrombotic events with other 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 *(see Section 4.2 DOSE AND METHOD OF ADMINISTRATION)*.

Neutralising Antibodies (Inhibitors)
Inhibitors have been reported with factor replacement therapy in the treatment of haemophilia B. Patients using ALPROLIX should be monitored for the development of factor IX inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported with ALPROLIX in the treatment of haemophilia B, including previously untreated patients. 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 (neutralising antibodies) should be suspected, and appropriate testing performed *(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Monitoring 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.

Monitoring 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 *(see Section 4.2 DOSE AND METHOD OF ADMINISTRATION)*. Factor IX results can be affected by the type of aPTT reagent used. Measurement with a one-stage clotting assay utilising 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 titre inhibitors).

Nephrotic Syndrome
Nephrotic syndrome has been reported following immune tolerance induction with factor IX products in haemophilia 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.

Use in the Elderly
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 individualised *(see Section 4.2 DOSE AND METHOD OF ADMINISTRATION)*.

Paediatric Use
Safety, efficacy, and pharmacokinetics of ALPROLIX have been evaluated in previously treated paediatric patients (PTPs) ages 12 to less than 18 years of age from Study 1 and under 12 years of age from Study 2. Safety and efficacy of ALPROLIX have been evaluated in previously untreated paediatric patients (PUPs) less than 18 years of age (median: 0.6 year; range: 0.08-2 years) from Study 4 see Section 4.8 UNDESIRABLE EFFECTS and Section 5.1 PHARMACODYNAMIC PROPERTIES).

No dose adjustment is required for ages 12 to less than 18 years of age (*see Section 5.2 PHARMACOKINETIC PROPERTIES and Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Efficacy and Safety*). In comparison with adolescents and adults, children less than 12 years of age may have a lower recovery and higher body-weight normalised factor IX clearance. These differences should be taken into account when dosing. Higher doses or more frequent dosing may be needed in patients less than 12 years of age (*see Section 5.2 PHARMACOKINETIC PROPERTIES – Paediatric pharmacokinetics*).

Use in patients with renal impairment
ALPROLIX has not been studied in patients with renal impairment.

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

Effect on Laboratory Tests
ALPROLIX temporarily corrects partial thromboplastin time (PTT) in patients with haemophilia B. No effect on normal prothrombin time was seen. There was no trend observed in coagulation activation parameters, including prothrombin fragment 1+ 2, D-dimer, and thrombin-antithrombin complex (TAT).

4.5 Interaction with Other Medicines and Other Forms of Interaction

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Category C
Animal reproductive studies have not been conducted with ALPROLIX. ALPROLIX has been shown to cross the placenta in small amounts in a placental transfer study in mice. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available. It is not known whether ALPROLIX can affect reproductive capacity. Fc fusion products, including eftrenonacog alfa, may pass through the placenta. The effects on the developing foetus are unknown.

ALPROLIX should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding
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. ALPROLIX should be used only if clinically indicated.

Fertility
No fertility studies have been conducted in animals with ALPROLIX. ALPROLIX has not been evaluated in animal reproductive studies.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Clinical Trials

Previously treated patients (PTPs)

ALPROLIX has been evaluated in three completed studies (Study 1, Study 2 and Study 3) which were conducted in previously treated patients (PTPs) with severe haemophilia B (≤ 2% endogenous FIX activity). A total of 153 subjects have been treated. Thirty (30) (19.6%) were paediatric 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 and older). There were 126 subjects (82.4%) treated for at least 52 weeks,107 subjects (69.9%) for at least 104 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 summarised in Table 3.

The most common adverse reactions in PTPs with an incidence ≥1% for ALPROLIX were headache, oral paraesthesia, 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 3: Adverse Drug Reactions reported for ALPROLIX in PTPs

MedDRA System Organ Class	MedDRA Preferred Term	N=153*		
		Number of Subjects N (%)	Frequency Category[1]	
			Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Nervous system disorders	Headache Dizziness Dysgeusia	2 (1.3) 1 (0.7) 1 (0.7)	Common	 Uncommon Uncommon
Gastrointestinal disorders	Paraesthesia oral Breath odour	2 (1.3) 1 (0.7)	Common	 Uncommon
General disorders and administration site conditions	Fatigue Infusion site pain	1 (0.7) 1 (0.7)		Uncommon Uncommon
Cardiac disorders	Palpitations	1 (0.7)		Uncommon

Renal and urinary disorders	Obstructive uropathy Haematuria Renal colic	2 (1.3) 1 (0.7) 1 (0.7)	Common	 Uncommon Uncommon
Vascular disorders	Hypotension	1 (0.7)		Uncommon
Metabolism and nutrition disorders	Decreased appetite	1 (0.7)		Uncommon

*The ALPROLIX clinical program included 153 previously treated patients (PTPs) on ALPROLIX therapy from 3 completed studies

1 ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - <1/10), Uncommon (≥ 1/1,000 - <1/100), Rare (≥ 1/10,000 - <1/1,000), Very Rare (<1/10,000)

Previously untreated patients (PUPs)

ALPROLIX safety was also evaluated in one completed study (Study 4) in 33 previously untreated patients (PUPs) with haemophilia B (≤2% endogenous FIX activity).
At enrolment, 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, the median number of weeks was 77.5 (range: 10.1-134.0 weeks).
The total number of exposure days (EDs) was 2,233.

The number of subjects 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 33 (6.1%) subjects treated with ALPROLIX. A total of 1 previously untreated patient (3.0%) developed a low-titre factor IX inhibitor. Adverse drug reactions in PUPs are summarised in Table 4.

Table 4 - Adverse Drug Reactions reported for ALPROLIX in PUPs

MedDRA System Organ Class	**MedDRA Preferred Term**	**N=33**	
		Number of Subjects N (%)	Frequency Category
			Common (≥1/100 to <1/10)
Blood and lymphatic system disorders	Factor IX inhibition*	1 (3.0)	Common
General disorders and administration site conditions	Injection site erythema	1 (3.0)	Common
Immune system disorders	Hypersensitivity*	1 (3.0)	Common

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

Post Marketing Experience
In post-marketing experience, the following adverse reactions have been reported:

Blood and Lymphatic Disorders: FIX inhibitor development
Immune System Disorders: Hypersensitivity, including anaphylaxis

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

No symptoms of overdose have been reported. For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor IX, ATC code: B02BD04
ALPROLIX (eftrenonacog alfa) (rhu) 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 eftrenonacog alfa 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 eftrenonacog alfa contains the hinge, CH2 and CH3 regions of IgG1. Eftrenonacog alfa contains 867 amino acids with a molecular weight of approximately 98 kilodaltons.

Eftrenonacog alfa is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterised. The HEK cell line expresses eftrenonacog alfa into a defined cell culture medium that does not contain any proteins derived from animal or human sources. Eftrenonacog alfa 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 15nm virus-retaining nano-filtration. No human or animal additives are used in the cell culture, purification, and formulation processes.

CAS registry number: 1270012-74-2

5.1 Pharmacodynamic Properties

Mechanism of Action
ALPROLIX (eftrenonacog alfa) is a long-acting, fully recombinant, fusion protein comprising human coagulation factor IX (FIX) covalently linked to the Fc domain of human IgG1, and produced by recombinant DNA technology.

FIX is an approximately 55 kDa vitamin K-dependent serine protease, which is an essential clotting factor in the coagulation cascade critical to the haemostasis 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.

Haemophilia 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 eftrenonacog alfa has similar structural and functional characteristics as endogenous FIX, and promotes haemostasis by correcting the deficiency of functional FIX.

The other portion of eftrenonacog alfa is the Fc region of human IgG1 which binds with the neonatal Fc receptor (FcRn). This receptor is expressed throughout life as part of a naturally occurring pathway that protects immunoglobulins from lysosomal degradation by cycling these proteins back into circulation, resulting in their long plasma half-life.

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.

Pharmacodynamics
Haemophilia B is a bleeding disorder characterized by a deficiency of functional clotting factor IX (FIX), which leads to a 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.

Clinical Efficacy and Safety
The safety, efficacy and pharmacokinetics of ALPROLIX were evaluated in two multicentre, open-label, pivotal studies in previously treated patients (PTPs): a Phase 3 study (Study 1) and a Phase 3 paediatric study (Study 2). Patients from Study 1 and Study 2 could subsequently enrol in a long-term extension study (Study 3). The safety and efficacy of ALPROLIX was also evaluated in previously untreated patients (PUPs) with haemophilia B (Study 4).

Study 1 compared the efficacy of each of two prophylactic treatment regimens to episodic (on-demand) treatment; determined haemostatic efficacy in the treatment of bleeding episodes; and determined haemostatic efficacy during perioperative management of subjects undergoing major surgical procedures. A total of 123 previously treated patients (PTPs) aged 12-71 with severe haemophilia B ($\leq$2% endogenous FIX activity) were followed for up to 77 weeks.

Sixty-three (63) subjects in the fixed weekly interval arm received ALPROLIX for routine prophylaxis starting at an initial dose of 50 IU/kg. The dose was adjusted to maintain trough between 1 and 3% above baseline or higher as clinically indicated to prevent bleeding. The median average weekly dose during the last 6 months on study in 58 subjects who were on study for at least 9 months was 40.7 IU/kg (interquartile range, 32.3, 54.1).

Twenty-nine (29) subjects in the individualised interval arm received ALPROLIX for routine prophylaxis at a dose of 100 IU/kg every 10 days, with the interval adjusted to maintain trough between 1 and 3% above baseline or higher as clinically indicated to

prevent bleeding. The median average interval during the last 6 months in 26 subjects who were on study for at least 9 months was 13.8 days (interquartile range, 10.5, 14.0).

Twenty-seven (27) subjects received ALPROLIX as needed for the treatment of bleeding episodes in the episodic (on-demand) treatment arm. Twelve (12) subjects received ALPROLIX for perioperative management in 14 major surgical procedures. Four subjects did not participate in the other arms.

Study 2 enrolled a total of 30 previously treated male paediatric patients with severe haemophilia B (≤2% endogenous FIX activity). Subjects were less than 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.

All 30 subjects were treated with ALPROLIX on an individualised prophylactic dose regimen starting with 50-60 IU/kg every 7 days, with adjustment of dose to a maximum of 100 IU/kg and dosing interval to a minimum of once weekly and a maximum of twice weekly. The median dosing interval was 6.99 days (interquartile range, 6.94 to 7.03) with no difference in the median average dosing interval between age cohorts. The median average weekly dose of ALPROLIX was 59.40 IU/kg (interquartile range, 52.95 to 64.78 IU/kg) for subjects <6 years of age and 57.78 IU/kg (interquartile range, 51.67 to 65.01 IU/kg) for subjects 6 to <12 years of age.

Study 3 was an open-label, multicentre, long-term study in previously treated patients with haemophilia B who had completed Study 1 or Study 2. The study evaluated the long-term safety and efficacy of rFIXFc for routine prophylaxis, on-demand treatment, and perioperative management with ALPROLIX. During the study, subjects, could change treatment groups. Of the 120 subjects in Study 3 (aged 3-63), 93 were from Study 1 and 27 were from Study 2.

Thirty-six subjects from Study 1 received individualised prophylaxis, 74 received weekly prophylaxis, 19 received personalised prophylaxis (for subjects in whom optimal prophylaxis could not be achieved with individualised or weekly prophylaxis), and 15 received episodic treatment with ALPROLIX. In addition, 16 subjects were also part of the surgery subgroup. The majority of subjects stayed on their treatment regimen throughout the extension study, with 21 subjects (22.6%) switching treatment regimens once or twice during the study. From the start of Study 1 to the end of Study 3, subjects had a median of 189 weeks of treatment (range <1 to 338). For evaluable subjects on prophylactic treatments in Study 3, the median average weekly dose was 48.46 IU/kg (interquartile range 39.88-61.07) for subjects in the weekly prophylaxis arm, 50.76 IU/kg (47.34-70.68) for subjects in the individualised prophylaxis arm, and 68.23 IU/kg (43.78-100.08) for subjects in the personalised prophylaxis arm. The median average dosing interval was 6.99 days (range 6.7 days to 7.8 days) for subjects in the weekly prophylaxis arm, 13.61 days (range 3.5 days to 21.3 days) for subjects in the individualised prophylaxis arm, and 6.61 days (range 3.3 days to 14.2 days) for subjects in the personalised prophylaxis arm.

Twenty-three subjects from Study 2 participated in weekly the prophylaxis arm, 5 subjects participated in the individualised prophylaxis arm and 2 subjects received personalised prophylaxis treatment with ALPROLIX. Three subjects (11.1%) switched

treatment regimens once during the study. From the start of Study 2 to the end of Study 3, subjects had a median of 150 (range: 16.9 to 251.1) cumulative weeks of treatment. For subjects in the 6 to <12 years of age cohort receiving individualised prophylaxis, the median average weekly dose was 67.70 IU/kg (range: 49.6 IU/kg to 139.2 IU/kg). The average weekly dose for the subject on personalised prophylaxis in the <6 years of age cohort was 59.66 IU/kg, and the average weekly dose for the subject in the 6 to <12 years of age cohort was 156.72 IU/kg.

Study 4 enrolled 33 previously untreated patients (PUPs) <18 years old with haemophilia B (≤2% endogenous FIX activity). The primary endpoint was the occurrence of inhibitor development. At enrolment, the median age was 0.6 years (range: 0.08-2 years), 78.8% of subjects were less than 1 year old, and the median weight was 9 kg (range: 4.6-17 kg). The overall median number of weeks on treatment was 83.01 (range: 6.7-226.7 weeks), and the overall median number of EDs was 76 days (range: 1-137 days) per subject. Subjects could be treated episodically (optional), until a prophylactic regimen was initiated.
Twenty-two subjects began on the episodic treatment regimen and received ALPROLIX as needed for the treatment of bleeding episodes. Of the 22 subjects who began the study on the episodic treatment regimen, 17 switched to prophylactic treatment for a total of 28 subjects who were ever on the prophylactic treatment regimen. The recommended starting dose was 50 IU/kg weekly for subjects on routine prophylaxis. Adjustments to the dose and dosing interval could be made based upon available incremental recovery data, subsequent FIX activity levels, level of physical activity, and bleeding pattern.
For those on prophylaxis regimen, the median average weekly dose was 57.96 IU/kg (range: 47.0-233.9 IU/kg) and the median average dosing interval was 7 days (range: 3.3-14.6 days).

Efficacy in Routine Prophylaxis

Study 1 (≥ 12 Years)
There was a reduction in annualised bleed rate (ABR) of 83% (76% to 89%) for subjects in the fixed weekly interval arm and a reduction of 87% (80% to 92%) for subjects in the individualised interval arm compared to the episodic (on demand) treatment arm based on a negative binomial model.

The median duration of treatment on study was 51.4 weeks (range <1-77). A comparison of the ABRs in subjects evaluable for efficacy is summarised in Table 5.

Table 5: Summary of Median (IQR)[1] Annualised Bleed Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age

Bleeding Episodes	Prophylaxis Fixed Weekly Interval (N=61)	Prophylaxis Individualised Interval (N=26)	Episodic (On Demand) (N=27)
Overall ABR	2.95 (1.01, 4.35)	1.38 (0.00, 3.43)	17.69 (10.77, 23.24)
Spontaneous ABR	1.04 (0.00, 2.19)	0.88 (0.00, 2.30)	11.78 (2.62, 19.78)
Traumatic ABR	0.99 (0.00, 2.13)	0.00 (0.00, 0.78)	2.21 (0.00, 6.81)

Joint ABR	1.11 (0.00, 4.01)	0.36 (0.00, 3.24)	13.58 (6.13, 21.61)

[1]Median (interquartile range, 25th and 75th percentiles)

Study 2 (<12 Years)

The median duration of treatment on study was 49.4 weeks (range 12 to 52). A summary of the median ABRs in paediatric subjects evaluable for efficacy is presented in Table 6.

Table 6: Summary of Median (IQR)[1] Annualised Bleed Rate (ABR) in Paediatric Subjects <12 Years of Age

Bleeding Episodes	<6 Years (N=15)	6 to <12 Years (N=15)	Total (< 12 Years) (N=30)
Overall ABR	1.09 (0.00, 2.90)	2.13 (0.00, 4.17)	1.97 (0.00, 3.13)
Spontaneous ABR	0.00 (0.00, 1.09)	0.00 (0.00, 2.09)	0.00 (0.00, 1.16)
Traumatic ABR	0.00 (0.00, 2.22)	1.06 (0.00, 2.21)	0.53 (0.00, 2.21)
Joint ABR	0.00 (0.00, 0.00)	1.06 (0.00, 2.09)	0.00 (0.00, 1.12)

[1]Median (interquartile range, 25th and 75th percentiles)

Study 3 (Extension Study)

The combined overall median annualised bleeding rates in adult and adolescent subjects (>12-66 years) are presented in

Table 7. The median duration of treatment on study was 208.0 weeks (range: 13.9 to 280).

Table 7: Summary of Median (IQR)[1] Annualized Bleeding Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age[2]

	Weekly Prophylaxis (N=51)	Individualised Prophylaxis (N=31)	Personalised Prophylaxis (N=16)	On-Demand (N=15)
Overall ABR	2.26 (0.40, 5.16)	1.85 (0.76, 4.00)	2.91 (1.14, 5.36)	11.64 (5.12, 18.54)
Spontaneous ABR	0.88 (0.00, 3.00)	0.73 (0.20, 1.85)	0.40 (0.00, 2.01)	3.41 (1.17, 16.95)
Traumatic ABR	0.52 (0.00, 1.85)	0.53 (0.00, 1.60)	1.14 (0.28, 2.90)	1.11 (0.00, 5.25)
Spontaneous Joint ABR	0.38 (0.00, 2.25	0.38 (0.00, 1.43)	0.30 (0.00, 1.37)	2.15 (0.58, 11.68)

[1]Median (interquartile range, 25th and 75th percentiles)
[2]Study subjects could change treatment groups during the study

The overall median annualised bleeding rates in paediatric subjects <12 years of age are presented in Table 8. All subjects from Study 2 were on a prophylactic regimen.

The median duration of treatment on Study 2 was 55 weeks (range: 7.9-177.0) in subjects <6 and 175.7 weeks (range:47.0-201.1) in subjects 6 to <12.

Table 8: Summary of Median (IQR)[1] Annualized Bleeding Rate (ABR) in Paediatric Subjects < 12 Years of Age[2]

	Weekly Prophylaxis	Individualised Prophylaxis	Personalised Prophylaxis
<6 Years	(N=13)	(N=0)	(N=1)
Overall ABR	1.04 (0.00, 2.28)	N/A	0.54
Spontaneous ABR	0.00 (0.00, 1.11)	N/A	0.54
Traumatic ABR	0.45 (0.00, 1.97)	N/A	0.00
Spontaneous Joint ABR	0.00 (0.00, 1.06)	N/A	0.00
6-12 Years	(N=10)	(N=5)	(N=1)
Overall ABR	1.14 (0.54, 2.34)	3.69 (3.54, 5.21)	3.13
Spontaneous ABR	0.13 (0.00, 1.68)	0.74 (0.59, 1.14)	0.00
Traumatic ABR	0.45 (0.00, 1.01)	2.36 (0.88, 2.55)	3.13
Spontaneous Joint ABR	0.00 (0.00, 1.40)	0.00 (0.00, 0.29)	0.00

[1]Median (interquartile range, 25th and 75th percentiles)[2] Study subjects could change treatment groups during the study

Study 4 (<18 Years) – PUPs

A summary of the median ABRs in PUPs evaluable for efficacy is presented in Table 9

Table 9 - Summary of Median (IQR)[1] Annualised Bleeding Rate (ABR) in PUPs <18 Years of Age

Bleeding Episode	Prophylactic (N=28)
Overall ABR	1.24 (0.00, 2.49)
Spontaneous ABR	0.00 (0.00, 0.00)
Traumatic ABR	0.91 (0.00, 1.80)
Spontaneous Joint ABR	0.00 (0.00, 0.00)

[1] Median (interquartile range, 25th and 75th percentiles)

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. Assessment of response to each injection was recorded by subjects at 8-12 hours post-treatment. A 4-point rating scale of excellent, good,

moderate, and no response was used to assess response. Bleeding episodes are summarised in
Table 10.

Table 10: Summary of Efficacy in Control of Bleeding

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 (IQR)		46.07 (32.86, 57.03)
Median total dose (IU/kg) to treat a bleeding episode (IQR)		46.99 (33.33, 62.50)
Response to first injection		(N=613)
	Excellent or good	513 (83.7%)
	Moderate	90 (14.7%)
	No response	10 (1.6%)

Study 2 (<12 Years)

A total of 60 bleeding events were observed during the study. Assessment of response to each injection was recorded by subjects at 8 to12 hours post treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Bleeding episodes are summarised in Table 11.

Table 11: **Summary of Efficacy in Control of Bleeding in Paediatric 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%)
Median average dose per injection (IU/kg) to treat a bleeding episode (IQR)				63.51 (48.92, 99.44)
Median total dose (IU/kg) to treat a bleeding episode (IQR)				68.22 (50.89, 126.19)
Response to first injection				(N=53)
	Excellent or good			47 (88.7%)
	Moderate			5 (9.4%)
	No response			1 (1.9%)

Study 3 (Extension Study)
In adult and adolescent subjects enrolled from Study 1, 342 (74.2%), 336 (87.0%), 135 (75.8%), and 603 (97.1%) of first injections evaluated for response were rated as excellent or good by the subjects receiving weekly prophylaxis, individualised prophylaxis, personalised prophylaxis, and episodic treatment, respectively.

In paediatric subjects enrolled from Study 2, 60 (81.1%) and 47 (82.5%) of first injections evaluated for response were rated as excellent or good for the subjects receiving weekly prophylaxis in the <6 years of age cohort and the 6 to <12 years of age cohort, respectively. For subjects receiving individualised prophylaxis, 25 (80.6%) of first injections evaluated for response were rated as excellent or good by the subjects in the 6 to <12 years of age cohort.

In subjects enrolled from Study 1, >96 % of bleeding episodes were controlled with ≤2 rFIXFc injections, and >84 % were controlled by 1 injection. In subjects enrolled from Study 2 receiving weekly or personalised prophylaxis, >98.7% and >66.7% of bleeding episodes were controlled with ≤2 injections of rFIXFc in the <6 years old cohort and the 6 to <12 years old cohort, respectively.

Study 4 (<18 Years) – PUPs

A summary of efficacy in control of bleeding in PUPs is presented in Table 12.

Table 12 - Summary of Efficacy in Control of Bleeding in PUPs <18 Years of Age

	Prophylactic (N=28)
# of bleeding episodes	58
# of Injections to treat bleeding episodes	
1 injection	51 (87.9%)
2 injections	5 (8.6%)
3 injections	1 (1.7%)
4 injections	1 (1.7%)
>4 injections	0
Median average dose per injection (IU/kg) to treat a bleeding episode (IQR)	71.92 (52.45, 100.81)
Median total dose (IU/kg) to treat a bleeding episode (IQR)	78.74 (53.57, 104.90)
Subject/caregiver's assessment of response to first injection[1,2]	
Excellent or good	37 (86%)
Moderate	5 (11.6%)
No response	1 (2.3%)
Investigator global assessment for total responses[3]	
Excellent	152 (95.6%)
Effective	7 (4.4%)
Partially effective	0
Ineffective	0

[1]Responses are based on number of first injections for a bleeding with an evaluation

[2]Excellent: abrupt pain relief and/or improvement in signs of bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring another injection in 1-2 days; Moderate: probable or slight beneficial effect and requiring more than 1 injection; None: no improvement, or condition worsening. Response evaluated at approximately 8 hours after treatment.

[3]Responses are based on physician's overall assessment of a subject's response to assigned regimen at each scheduled postbaseline visit

Efficacy in Perioperative Management (Surgical Prophylaxis)

Major Surgeries

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

Haemostasis was assessed post-operatively by the investigator using a 4-point scale of excellent, good, fair, and none. The haemostatic 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.

Haemostatic response to dosing during surgery and post-operatively for Study 1 and Study 3 are summarised in Table 13.

Table 13: **Summary of Haemostatic Response During Surgery and Post-Operatively**

Major Surgery	Number of Procedures (Number of Subjects)	Response			
		Excellent	Good	Fair	Poor/None
Ablation of Liver Lesion	1 (1)	1			
Arthroscopy	2 (2)	2			
Closure of Rectal Fistula	1 (1)	1			
Craniotomy[1]	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 Removal of External Ilizarov Fixa	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 haemostatic assessment in 62 minor surgical procedures in 37 subjects was conducted in Study 1, Study 2, and Study 3. Haemostatic response was assessed for 38 minor surgeries; 36 minor surgeries were rated as excellent or good and 2 as fair.

5.2 Pharmacokinetic properties

The pharmacokinetics of ALPROLIX (eftrenonacog alfa) [rFIXFc] versus BeneFIX (nonacog alfa) [rFIX] were evaluated following a 10-minute IV infusion in 22 evaluable subjects (≥19 years) in 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 for ALPROLIX were estimated based on the plasma FIX activity over time profile. A central laboratory analysed 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 infusion, e.g., at 10 minutes from the start of the dosing. The geometric mean increase in circulating FIX activity from pre-infusion 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 14.

Table 14: **Pharmacokinetic Parameters of ALPROLIX (rFIXFc) and BeneFIX (rFIX)**

Pharmacokinetic Parameters[1]	**ALPROLIX (95% CI)**	**BeneFIX (95% CI)**	**Ratio of ALPROLIX to BeneFIX (95% CI)**
	N=22	**N=22**	**N=22**
Cmax (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)
t1/2α (h)	**5.03** (3.20, 7.89)	**2.41** (1.62, 3.59)	**2.09** (1.18, 3.68)
t1/2β (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)
Vss (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% (days)	**11.22** (10.20, 12.35)	**5.09** (4.58, 5.65)	**2.21** (2.04, 2.39)

[1] Pharmacokinetic parameters derived using a two compartment model are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; Cmax = maximum activity; AUC = area under the FIX activity time curve; t1/2α = distribution half-life; t1/2β = elimination half-life; CL = clearance; MRT = mean residence time; Vss = volume of distribution at steady-state

Paediatric Pharmacokinetics

Pharmacokinetic parameters of ALPROLIX (rFIXFc) were determined for adolescents 12 to less than 18 years of age in Study 1, and for children less than 12 years of age in Study 2 (*see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use*).

Pharmacokinetic parameters were evaluated following a 10-minute IV infusion in 11 evaluable adolescents who received a single dose of ALPROLIX. Pharmacokinetic samples were collected pre-dose and at multiple time points up to 336 hours (14 days) post-dose. In Study 2, pharmacokinetic parameters were evaluated following a 10-minute IV infusion in 24 evaluable children (less than 12 years of age) who received a single dose of ALPROLIX. Pharmacokinetic samples were collected pre-dose and at 7 time points up to 168 hours (7 days) post-dose. Pharmacokinetic parameters for ALPROLIX were estimated based on the plasma FIX activity over time profile. A central laboratory analysed all of the pharmacokinetic 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 15 presents the pharmacokinetic parameters calculated from the paediatric data of 35 subjects less than 18 years of age. Compared to adults, incremental recovery appeared to be lower and body weight normalised clearance appeared to be higher in children less than 12 years of age. This may result in a need for dose adjustments in children less than 12 years of age (*see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use*).

Table 15: Comparison of Pharmacokinetic Parameters of ALPROLIX (rFIXFc) by Age Category

Pharmacokinetic Parameters[1]	Study 2		Study 1
	<6 years (2, 4)[2]	6 to <12 years (6, 10)[2]	12 to <18 years (12, 17)[2]
	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]Pharmacokinetic parameters derived from non-compartmental analysis are presented in Geometric Mean (95% CI)

[2] Age range of subjects in each age category

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; Vss = volume of distribution at steady-state

Population Pharmacokinetics

A three-compartment population pharmacokinetic model was developed based on pharmacokinetic data from 153 subjects, from 1 to 71 years old and weighing between 13.5 kg and 186.7 kg, in three clinical studies (12 subjects in a phase 1/2a study, 123 subjects in Study 1, and 26 subjects in Study 2). The estimate of CL of ALPROLIX for a typical 70 kg adult is 2.30 dL/h, volume of central compartment (V1) is 66.4 dL, and V_{ss} is 194.8 dL. The model was used to predict the activity time profile following dosing with ALPROLIX in patients with severe haemophilia B (see Table 16, Table 17 and Table 18*).*

Table 16: Predicted FIX Activity Following a Single Dose of ALPROLIX[1] to Adults and Adolescents ≥ 12 Years of Age

Dose (IU/kg)	End of Infusion	12 hours	24 hours (Day 1)	36 hours	48 hours (Day 2)	72 hours (Day 3)	Day 5	Day 7	Day 10	Day 14
	Median [5th, 95th]									
50	**52.0** [31.8, 82.0]	**21.7** [15.0, 31.0]	**15.2** [10.2, 21.5]	**11.3** [7.50, 16.5]	**8.40** [5.50, 12.5]	**5.50** [3.59, 8.25]	**3.02** [1.88, 4.65]	**1.93** [0.99, 3.12]	**1.07** [0.345, 1.95]	**0.495** [0.0829, 1.17]
100	**104.0** [63.6, 164]	**43.4** [30.0, 62.0]	**30.4** [20.4, 42.9]	**22.6** [15.0, 32.9]	**16.8** [11.0, 24.9]	**11.0** [7.18, 16.5]	**6.03** [3.77, 9.29]	**3.85** [1.98, 6.24]	**2.13** [0.691, 3.89]	**0.991** [0.166, 2.34]

[1]*See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.*

Table 17: Predicted FIX Activity Following a Single Dose of ALPROLIX1 to paediatric patients 6-<12 Years of Age

Dose (IU/kg)	End of Infusion	12 hours	24 hours (Day 1)	36 hours	48 hours (Day 2)	72 hours (Day 3)	Day 5	Day 7	Day 10	Day 14
	Median [5th, 95th]									
50	**36.5** [22.7, 57.5]	**16.1** [11.0, 22.6]	**11.5** [7.60, 16.4]	**8.70** [5.70, 12.6]	**6.65** [4.33, 9.65]	**4.49** [2.95, 6.60]	**2.59** [1.64, 3.83]	**1.72** [0.975, 2.66]	**0.995** [0.386, 1.71]	**0.503** [0.105, 1.07]
100	**73.1** [45.4, 115.0]	**32.1** [21.9, 45.1]	**22.9** [15.2, 32.7]	**17.4** [11.4, 25.1]	**13.3** [8.67, 19.3]	**8.98** [5.90, 13.2]	**5.17** [3.29, 7.66]	**3.45** [1.95, 5.32]	**1.99** [0.773, 3.41]	**1.01** [0.210, 2.14]

[1]*See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.*

Table 18: Predicted FIX Activity Following a Single Dose of ALPROLIX1 to paediatric patients < 6 Years of Age

Dose (IU/kg)	End of Infusion	12 hours	24 hours (Day 1)	36 hours	48 hours (Day 2)	72 hours (Day 3)	Day 5	Day 7	Day 10	Day 14
	Median [5th, 95th]									
50	**27.3** [16.9, 43.8]	**12.4** [8.65, 17.9]	**9.05** [6.15, 13.0]	**7.00** [4.73, 10.0]	**5.45** [3.66, 7.90]	**3.80** [2.53, 5.55]	**2.26** [1.51, 3.30]	**1.56** [0.945, 2.33]	**0.94** [0.405, 1.54]	**0.496** [0.121, 0.991]
100	**54.6** [33.8, 87.5]	**24.9** [17.3, 35.7]	**18.1** [12.3, 26.0]	**14.0** [9.46, 20.0]	**10.9** [7.32, 15.8]	**7.60** [5.06, 11.1]	**4.51** [3.03, 6.60]	**3.12** [1.89, 4.65]	**1.88** [0.811, 3.08]	**0.991** [0.242, 1.98]

[1]*See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.*

Measured FIX activity in 14 subjects undergoing surgical procedures in a clinical study was consistent with the values predicted by the population PK model. A sample perioperative dosing regimen to achieve target FIX levels for adults and adolescents, as simulated by this model, is shown in Table .

Table 19: Predicted FIX Activity for a Sample Perioperative Dosing Regimen1 for Adults and Adolescents ≥12 Years of Age

Day at Dose[2]	Time at Dose (hr)	Dose (IU/kg)	Trough[3] (IU/dL) Median [25th, 75th]
0	0	100	NA
0	8	80	49.7 [42.3, 56.7]
1	24	80	60.6 [51.9, 70.7]
2	48	80	57.1 [48.3, 66.2]
3	72	80	58.4 [49.4, 67.9]
5	120	70	39.5 [33.0, 46.6]
7	168	70	33.6 [28.0, 39.9]
9	216	70	31.3 [26.0, 37.4]
11	264	70	30.2 [24.8, 36.5]
13	312	70	29.3 [24.0, 35.7]

[1] *See Section 4.2 DOSE AND METHOD OF ADMINISTRATION*

[2] Day 0 = day of surgery

[3] Target FIX trough activity levels per WFH 2008 and WFH 2012

ALPROLIX has been evaluated in 153 male haemophilia B (PTP) patients from 1 to 71 years of age (*see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Use in the elderly*) and weighing between 13.5 to 186.7kg. Body weight has an impact on

the pharmacokinetics of ALPROLIX. Age does not provide any further impact beyond that provided by body weight.

No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on ALPROLIX disposition.

Race and ethnicity have no observed effect on the pharmacokinetics of ALPROLIX.

5.3 Preclinical Safety Data

Genotoxicity
ALPROLIX has not been evaluated in mutagenicity or chromosomal aberration assays since it is a replacement protein factor for coagulation.

Carcinogenicity
No animal studies investigating carcinogenicity effects of ALPROLIX have been conducted since it is a replacement factor for coagulation activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

When reconstituted with the provided diluent, the product contains the following excipients:

Sucrose
Sodium chloride
Histidine
Mannitol
Polysorbate 20
Water for injection

6.2 Incompatibilities

For intravenous administration only after reconstitution.

6.3 Shelf Life

4 years

The reconstituted product can be stored at room temperature (30°C) for 6 hours. Protect product from direct sunlight. If product is not used within 6 hours, it must be discarded. The appearance of the reconstituted product should be clear to slightly opalescent and colourless.

6.4 Special Precautions for Storage

Protect from light. Unopened vials should be stored under controlled refrigeration (2°C - 8°C). Do not freeze.

The product may be stored at room temperature (up 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 period.

For storage conditions after reconstitution of the medicine, see Section 6.3.

6.5 Nature and Contents of Container

Each pack contains a powder vial (type 1 glass) with a stopper (butyl) and a flip-off seal (aluminium), 5 mL diluent in a pre-filled syringe (type 1 glass) with a plunger stopper (butyl), a tipcap (butyl), and a sterile vial adapter reconstitution device.

ALPROLIX is available in 6 vial sizes - 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU. Factor IX activity in International Units is stated on the label of each ALPROLIX carton and vial.

6.6 Special Precautions for Disposal and Other Handling

Consult the Directions for Use provided at the end of this document for detailed reconstitution instructions.

Dispose of all the materials in accordance with local requirements.

7 MEDICINE SCHEDULE

General Sale

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

3 September 2015

10 DATE OF REVISION OF THE TEXT

20 June 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change of sponsor

ALPROLIX® (all-pro-liks)

Eftrenonacog alfa (rhu)

RECOMBINANT COAGULATION FACTOR IX FC FUSION PROTEIN 250, 500, 1000, 2000, 3000, 4000 IU/VIAL FOR IV INFUSION

Directions for Use

Read all the instructions before you start. If you have any questions about this guide, ask your doctor or pharmacist. Your healthcare provider should show you or your caregiver how to reconstitute and administer ALPROLIX the first time ALPROLIX is used.

There are 5 steps, explained in this guide:

A. Setting up

B. Reconstituting the injection

C. Pooling

D. Giving the injection

E. Post-Infusion Care & Disposal

Take time to read through each section and keep this leaflet with your medicine as a reminder of what to do.

A. Setting up

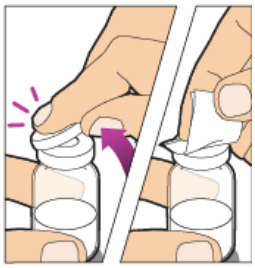
A1. First ensure that your work area is clean.

A2. Collect everything you will need. Check the expiry date on the ALPROLIX kit. If it is out of date, do not use it and contact your pharmacy immediately. If refrigerated, allow the vial of ALPROLIX and the pre-filled diluent syringe to warm to room temperature (15°C to 30ºC) for approximately 30 minutes. Do not use heat sources (for example, hot water or a heater) to warm the contents.

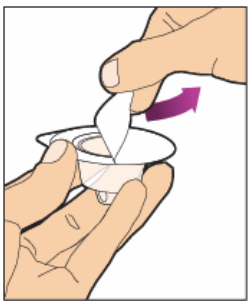
A3. Wash your hands thoroughly with soap and water before performing the following procedures.

A4. Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

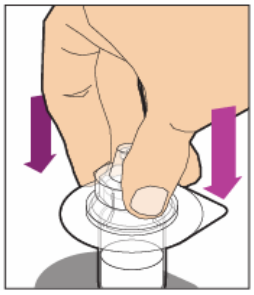
A5. Remove the plastic cap from the ALPROLIX vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.



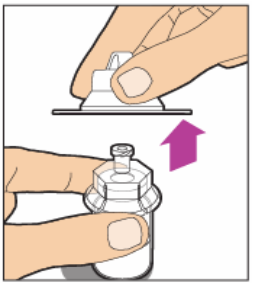
A6. Completely remove the backing from the vial adapter package by peeling back the lid. **Do not remove the vial adapter from the package or touch the inside of the package or the adapter.**



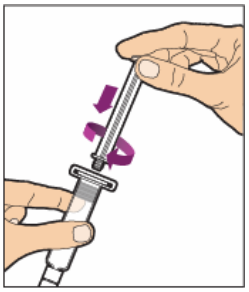
A7. Keep the vial on a flat surface. Hold the vial adapter package with one hand and using the other hand, place the vial adapter over the vial. The spike should be placed directly above the centre of the rubber stopper. Push the vial adapter straight down until the adapter spike punctures the centre of the vial stopper and is fully inserted.



A8. Lift the package cover away from the vial adapter and discard the cover.

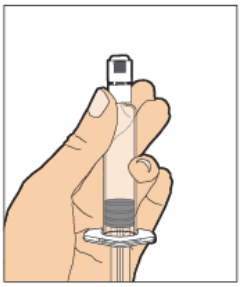


A9. Take the plunger rod and syringe out of the package. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn in a clockwise direction until it is securely attached. Only use the diluent syringe provided to reconstitute the drug product.

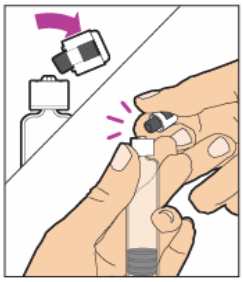


B. Reconstituting the injection

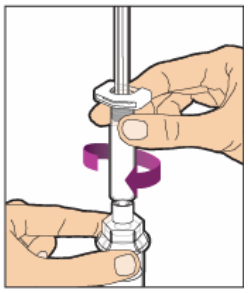
B1. With one hand, hold the diluent syringe right under the cap, and with the cap pointing up. Make sure you are holding the diluent syringe by the ridged part directly under the cap. **Do not use if the cap has been removed or is not securely attached.**



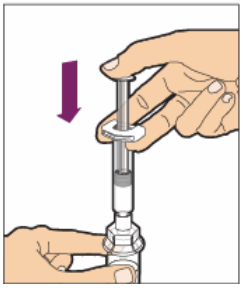
B2. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe**. Do not touch the glass tip of the syringe or the inside of the cap.**



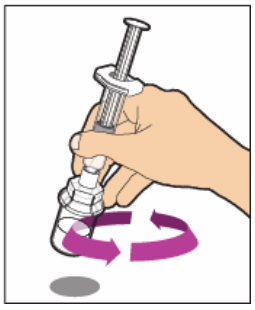
B3. Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe in a clockwise direction until it is securely attached to the adapter.



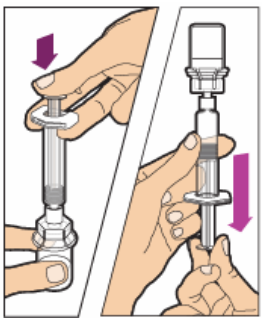
B4. Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.



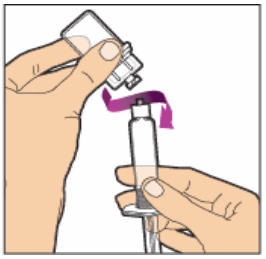
B5. With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. The appearance of the solution should be clear to slightly opalescent and colourless. **Do not shake. Do not use the reconstituted ALPROLIX if it contains visible particles or is cloudy.**



B6. 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.**



B7. 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.**



B8. Your ALPROLIX is now ready to be connected to your infusion tubing set. See section D below. Reconstituted ALPROLIX should be administered as soon as possible.

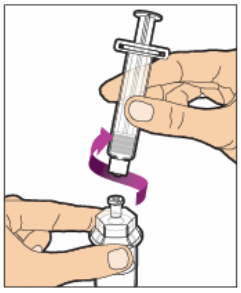
C. Pooling

If you are using two or more reconstituted vials of ALPROLIX, you can follow these pooling steps.

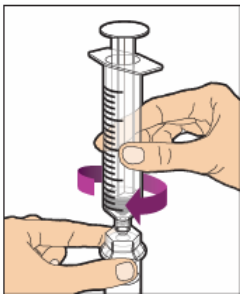
C1. Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a large luer lock syringe.

C2. Do not detach the diluent syringe or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial (with vial adapter attached).

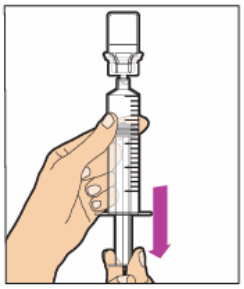
C3. Remove the diluent syringe from the vial adapter by turning it counter-clockwise until it is completely detached



C4. Attach a separate large luer lock syringe by turning clockwise until it is securely attached.



C5. 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.

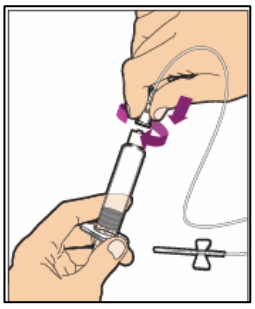


D. Giving the injection

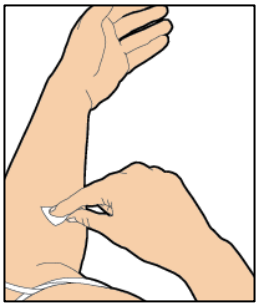
For Intravenous Use only after Reconstitution
ALPROLIX is administered by intravenous (IV) infusion after reconstitution of the drug powder with the diluent.

Do not administer reconstituted ALPROLIX if it contains visible particles, is discoloured, or is cloudy.

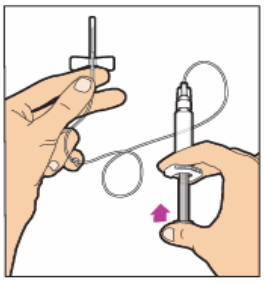
D1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. **Do not administer reconstituted ALPROLIX in the same tubing or container with other medicinal products. Do not remove the protective needle cover until you are ready to insert the needle (see section D4 below)**



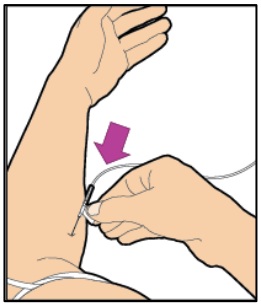
D2. Apply a tourniquet and clean the skin area where you will perform the infusion using an alcohol wipe.



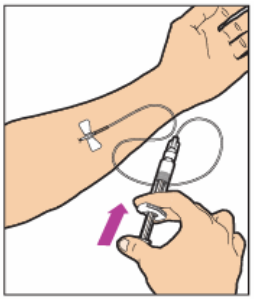
D3. Depress the plunger until all air is removed from the syringe and ALPROLIX has reached the end of the infusion set tubing. Do not push ALPROLIX through the needle.



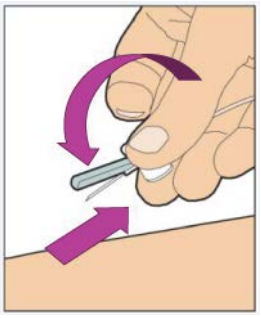
D4. Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



D5. 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.

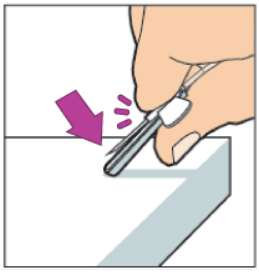


D6. After infusing ALPROLIX, flip the safety shield towards the needle. Remove the infusion set.

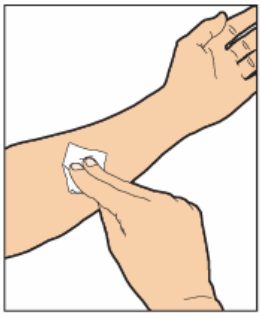


E. Post-Infusion Care & Disposal

E1. 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.



E2. Use a sterile gauze to put pressure on the infusion site for several minutes. Apply an adhesive bandage if necessary.



E3. A sharps bin should be used for disposal of all unused solution, empty vials and used needles and syringes.