AUSTRALIAN PRODUCT INFORMATION – ALPROLIX (EFTRENONACOG ALFA) (RHU) POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Eftrenonacog alfa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains nominally 250, 500, 1000, 2000, 3000 or 4000 International Units (IU) of eftrenonacog alfa.

Each pre-filled syringe contains 5 mL of solvent.

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.

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

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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 (sterile sodium chloride solution 0.325%) 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. Consult the Directions for Use provided at the end of this document for detailed reconstitution instructions.

Each vial of ALPROLIX has the recombinant FIX potency in International Units stated on the label. It is recommended that prescribed doses of ALPROLIX are expressed as "International Units", written in full.

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	50-80	50-80 IU/kg A single infusion may be sufficient. Repeat as needed after 24-48 hours.
Major	60-100 (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, 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 in 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 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).

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 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 5.1 PHARMACODYNAMIC PROPERTIES (Clinical Trials).

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 Trials). 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).

Effects 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in 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.

Use in lactation

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 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 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	2 (1.3)	Common	
	Dizziness	1 (0.7)		Uncommon
	Dysgeusia	1 (0.7)		Uncommon
Gastrointestinal disorders	Paresthesia oral	2 (1.3)	Common	
	Breath odour	1 (0.7)		Uncommon
General disorders and administration site conditions	Fatigue	1 (0.7)		Uncommon
	Infusion site pain	1 (0.7)		Uncommon
Cardiac disorders	Palpitations	1 (0.7)		Uncommon
Renal and urinary disorders	Obstructive uropathy	2 (1.3)	Common	
	Haematuria	1 (0.7)		Uncommon
	Renal colic	1 (0.7)		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 to 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-titer 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 shown in Table 4 occurred in a single previously untreated subject while on ALPROLIX, after 10 Eds. This subject discontinued ALPROLIX due to the adverse drug reactions.

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

No symptoms of overdose have been reported. For information on the management of overdose, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 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.

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.

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.

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.

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.

Clinical trials

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 (≤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 dosing interval between age cohorts. The median 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.

Subject treatment regimes and doses are shown in Table 5 and Table 6.

From Study 1, 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). Fifteen subjects were part of the surgery subgroup.

Table 5 - Treatment groups, dose and dosage intervals for subjects from Study 1 who participated in Study 3

	Individualised prophylaxis	Weekly prophylaxis	Personalised prophylaxis	Episodic treatment
Number of subjects	74	36	19	15
Average[1] Weekly Dose	50.76 IU/kg (47.34-70.68)	48.46 IU/kg (39.88 – 61.07)	68.23 IU/kg (43.78 – 100.08)	N/A
Average[1] dosing interval	13.61 days (3.9 – 21.3)	6.99 days (6.7 – 7.8)	6.61 days (3.3 – 14.2)	N/A

[1]Median (range)

The majority of subjects from Study 2 stayed on their treatment regimen throughout the extension study, with 3 subjects (11.1%) switching treatment regimens once or twice 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.

Table 6 - Treatment groups, dose and dosage intervals for subjects from Study 2 who participated in Study 3

	Individualised prophylaxis	Weekly prophylaxis	Personalised prophylaxis
	Age of subjects (<6 years)		
Number of subjects (Age <6)	-	13	1
Average[1] Weekly Dose	N/A	64.64 IU/kg (41.2 – 82.5)	59.66 IU/kg (59.7 – 59.7)
Average[1] dosing interval	N/A	7.0 days (6.8 – 7.2)	4.5 days (4.5 – 4.5)

	Individualised prophylaxis	Weekly prophylaxis	Personalised prophylaxis
	Age of subjects (6-<12 years)		
Number of subjects (Age 6-<12))	5	10	1
Average[1] Weekly Dose	67.70 IU/kg (47.6-139.2)	59.96 IU/kg (44.2 – 81.8)	156.72 IU/kg (156.7 –156.7)
Average[1] dosing interval	10.20 days (5.2 – 13.2)	7.02 days (6.9 – 7.5)	4.11 days (4.1 – 4.1)

[1]Median (range)

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 7.

Table 7 - 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)

Bleeding Episodes	Prophylaxis Fixed Weekly Interval (N=61)	Prophylaxis Individualised Interval (N=26)	Episodic (On Demand) (N=27)
Traumatic ABR	0.99 (0.00, 2.13)	0.00 (0.00, 0.78)	2.21 (0.00, 6.81)
Spontaneous 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 8.

Table 8 - 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)
Spontaneous 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 adults and adolescent subjects (>12-66 years) are presented in Table 9. The median duration of treatment on study was 208.0 weeks (range: 13.9 to 280).

Table 9 - Summary of Median (IQR)[1] Annualised Bleed Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age[2]

Bleeding Episodes	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)

Bleeding Episodes	Weekly Prophylaxis (N=51)	Individualised Prophylaxis (N=31)	Personalised Prophylaxis (N=16)	On Demand (N=15)
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 10. The median duration of treatment on Study 2 was 55 weeks (range: 7.9-177.0) in subjects <5 and 175.7 weeks (range: 47.0-201.1) in subjects 6 to <12.

Table 10 - Summary of Median (IQR)[1] Annualised Bleed Rate (ABR) by Treatment Arm in Subjects <12 Years of Age[2]

Bleeding Episodes	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

Study 4 (<18 Years) – PUPs

A summary of the median ABRs in PUPs evaluable for efficacy is presented in Table 11

Table 11 - 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 12.

Table 12 - 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%)

Bleeding episodes	**(N=636)**

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 13.

Table 13 - 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)

Adult and adolescent study (12 to 71 years)

A total of 636 bleeding events were observed by 114 subjects in the fixed weekly interval prophylaxis, individualized interval prophylaxis, and the episodic (on-demand) arms. The median total dose to treat a bleeding episode was 47.0 IU/kg (interquartile range: 33.3, 62.5). Assessment of response to each injection was recorded by subjects at 8-12 hours after treatment. Efficacy in control of bleeding episodes is summarized in Table 14.

Table 14 - Efficacy in Control of Bleeding in Adults and Adolescents

Bleeding episodes	(N=636)
Number of injections to treat bleeding episodes	
1 injection	575 (90.4%)
2 injections	44 (6.9%)
3 injections	17 (2.7%)
Response* to first injection	(N=613)
Excellent or good	513 (83.7%)
Moderate	90 (14.7%)
None	10 (1.6%)

*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 one injection; None: no improvement, or worsening. Response evaluated at approximately 8 hours after treatment.

Paediatric study (1 to 11 years)

A total of 60 bleeding events were observed by 20 subjects during the study. The median total dose to treat a bleeding episode was 68.2 IU/kg (interquartile range: 50.9, 126.2). Assessment of response to each injection was recorded by subjects at 8 to12 hours post treatment. Efficacy in control of bleeding episodes is summarized in Table 15.

Table 15- Efficacy in Control of Bleeding in Paediatric Subjects

	1 to 5 Years	6 to 11 Years	Total (1 to 11 Years)
Bleeding episodes	(N=22)	(N=38)	(N=60)
Number 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%)
Response* to first injection		(N=53)	
Excellent or good		47 (88.7%)	
Moderate		5 (9.4%)	
None		1 (1.9%)	

Study 4 (<18 Years) – PUPs

A summary of efficacy in control of bleeding in PUPs is presented in Table 16.

Table 16 - 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 (21 Adults and adolescents, and 1 paediatric patient <12 years of age). Of the 35 major surgeries, 28 surgeries (80.0%) required a single pre-operative 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 17.

Table 17 - Summary of Haemostatic Response During Surgery and Post-Operatively

		Response			
Major Surgery	**Number of Procedures (Number of Subjects)**	**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			
Percutaneous-Ablation of Hepatic Carcinoma	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			
Transarterial Chemoembolisation	3 (1)	3			
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 forty-three 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 18.

Table 18 - 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; 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

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 19 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 19 - 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)

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
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)
t½ (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)
Vss (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; V_{ss} = volume of distribution at steady-state

Population Pharmacokinetics

A three-compartment population pharmacokinetic model was developed based on pharmacokinetic data from 161 subjects, from 2 to 76 years old and weighing between 12.5 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 20, Table 21, Table 22).

Table 20 - 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]

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]									

[1] See Section 4.2 DOSE AND METHOD OF ADMINISTRATION

Table 21 - Predicted FIX Activity Following a Single Dose of ALPROLIX[1] 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 22 - Predicted FIX Activity Following a Single Dose of ALPROLIX[1] 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 23.

Table 23 - Predicted FIX Activity for a Sample Perioperative Dosing Regimen[1] 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 Dosage and Administration
[2] Day 0 = day of surgery
[3] Target FIX trough activity levels per WFH 2008 and WFH 2012

ALPROLIX has been evaluated in 161 male haemophilia B patients from 2 to 76 years of age (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in the elderly) and weighing between 12.5 to 186.7 kg. 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

Powder

Sucrose

Histidine

Mannitol

Polysorbate 20

Solvent

Sodium chloride

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

4 years. The expiry date can be found on the packaging.

Reconstituted solution

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. Do not freeze the pre-filled syringe.

For storage conditions of the reconstituted medicinal product, see Section 6.3 SHELF LIFE.

6.5 NATURE AND CONTENTS OF CONTAINER

Powder

Vial (type I glass) with a stopper (butyl) and a flip-off seal (aluminium). ALPROLIX is available as 6 vial sizes - containing 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 or 4000 IU. Factor IX activity in International Units is stated on the label of each ALPROLIX carton and vial.

Solvent

5 mL diluent in a pre-filled syringe (type I glass) with a plunger stopper (butyl), a tipcap (butyl), and a sterile vial adaptor reconstitution device.

Pack size

- 1 vial with powder
- 1 pre-filled syringe with solvent
- 1 vial adapter

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements. The syringe and needle cap should be disposed of in a sharps container.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

CAS number

1270012-74-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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12-24 Talavera Road
Macquarie Park NSW 2113
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9 DATE OF FIRST APPROVAL

1 May 2014

10 DATE OF REVISION

04 November 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Remove specific excipient, sodium as per TGO91
4.4	Included warning specific to untreated paediatric patients (PUPs)
4.8	Included adverse events specific to PUPs
5.1	Included clinical data specific to PUPs
4.4	Included warning specific to untreated paediatric patients (PUPs)