PRODUCT INFORMATION

ALPROLIX (eftrenonacog alfa) (rhu) powder and solvent for solution for injection.

NAME OF THE MEDICINE

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

DESCRIPTION

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.

Each single-use vial contains nominally 250, 500, 1000, 2000, or 3000 International Units (IU) of eftrenonacog alfa. When reconstituted with the provided diluent, the product contains the following excipients: sucrose, sodium chloride, histidine, mannitol, and polysorbate 20.

For intravenous administration only after reconstitution.

PHARMACOLOGY

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.

Pharmacokinetics

The pharmacokinetics of ALPROLIX [rFIXFc] versus BeneFIX (nonacog alfa) [rFIX)] were evaluated following a 10-minute IV infusion in 22 evaluable subjects (≥19 years) from a clinical study. 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 1.

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

1 Pharmacokinetic parameters are presented in Geometric Mean (95% CI)

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

A population pharmacokinetic (PK) model was developed based on pharmacokinetic data from 135 subjects, from 12 to 76 years old and weighing between 45kg and 186.7kg, in two clinical studies (12 subjects in a phase 1/2a study and 123 subjects in a phase 3 study). The population estimate for the typical CL of ALPROLIX is 2.39 dL/h, typical volume of central compartment (V1) is 71.4 dL, and V_{ss} is 198.3 dL. The model was used to predict the activity time profile following dosing with ALPROLIX in patients with severe haemophilia B *(see Table 2).*

Table 2: Predicted FIX Activity Following a Single Dose of ALPROLIX[1]

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	50.8 [30.4, 84.5]	21.1 [13.5, 33.6]	14.8 [9.8, 22.7]	10.9 [6.8, 17.1]	8.5 [5.1, 3.2]	5.6 [3.1, 9.3]	3.1 [1.4, 5.6]	1.9 [0.8, 3.7]	1.1 [0.3, 2.3]	0.6 [0, 1.4]
100	102.0 [60.8, 169.0]	42.3 [26.8, 67.3]	29.5 [19.6, 45.5]	21.8 [13.7, 34.1]	17.0 [10.5, 26.6]	11.1 [6.2, 18.5]	6.1 [3.1, 11.0]	3.9 [1.8, 7.3]	2.2 [0.8, 4.6]	1.1 [0.1, 2.6]

1 See DOSAGE AND 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, as simulated by this model, is shown in Table 3.

Table 3: Predicted FIX Activity for a Sample Perioperative Dosing Regimen[1]

Day at Dose[2]	Time at Dose (hr)	Dose (IU/kg)	Trough[3] (IU/dL) Median [5th, 95th]
0	0	100	NA
0	8	80	47.3 [30.7, 73.5]
1	24	80	58.5 [38.6, 89.2]
2	48	80	55.3 [36.4, 85.1]
3	72	80	57.5 [38.0, 88.6]
5	120	70	39.8 [25.0, 66.4]
7	168	70	33.5 [20.6, 55.4]
9	216	70	31.0 [18.9, 50.4]
11	264	70	29.7 [18.6, 50.0]
13	312	70	29.3 [17.2, 47.8]

1 *See Dosage and Administration*
2 Day 0 = day of surgery
3 Target FIX trough activity levels per WFH 2008 and WFH 2012

The safety, efficacy and pharmacokinetics of ALPROLIX have been evaluated in 135 male haemophilia B patients from 12 to 76 years old and weighing between 45kg and 186.7kg. Age had no effect on the pharmacokinetics of ALPROLIX and body weight had a minor impact (3%).

The pharmacokinetics of ALPROLIX have not been evaluated in paediatric patients with haemophilia B below the age of 12.

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.

CLINICAL TRIALS

The safety, efficacy and pharmacokinetics of ALPROLIX was evaluated in a multicentre, open-label, prospective study that 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 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 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.

Efficacy in Routine Prophylaxis

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 4.

Table 4: Summary of Median (IQR*) Annualised Bleed Rate (ABR) by Treatment Arm

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

**IQR = interquartile range*

Efficacy in Control of Bleeding

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. Bleeding episodes are summarised in Table 5.

Table 5: Summary of Efficacy in Control of Bleeding

New Bleeding episodes	(N= 636)	
# of Injections to treat bleeding episodes	1 injection 2 injections 3 injections	575 (90.4%) 44 (6.9%) 17 (2.7%)
Median 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 Moderate No response	513 (83.7%) 90 (14.7%) 10 (1.6%)

Efficacy in Perioperative Management (Surgical Prophylaxis)

Fourteen (14) major surgical procedures were performed in 12 subjects. Haemostasis was assessed at 24 hours post-operatively by the investigator using a 4-point scale of excellent, good, fair, and none. The haemostatic response was rated as excellent or good in 100% of major surgeries. There was no clinical evidence of thrombotic complications in

any of the subjects. Haemostatic response to dosing during surgery and post-operatively is summarised in Table 6.

Table 6: Summary of Haemostatic Response During Surgery and Post-Operatively

		Response			
Major Surgery	**Number of Procedures (Number of Subjects)**	**Excellent**	**Good**	**Fair**	**Poor/None**
Total Knee Replacement	5 (5)	4	1		
Arthroscopic Procedure	1 (1)	1			
Arthroscopic Ankle Fusion	1 (1)	1			
Closure of Rectal Fistula	1 (1)	1			
External Fixation of Knee	1 (1)	1			
Tendon Transfer	1 (1)	1			
I & D[1] of Dental Abscess with Extractions	1 (1)	1			
I & D[1] Pilonidal Cyst	1 (1)	1			
Debridement, Partial Amputation	1 (1)	1			
Amputation of Finger	1 (1)	1			
Minor surgery[2]	15 (13)	10	1	1	

[1] Incision and Drainage
[2] Assessment of response not provided for 3 minor surgeries

INDICATIONS

ALPROLIX is a long-acting anti-haemophilic factor (recombinant) indicated in adults and children (≥12 years) 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)

CONTRAINDICATIONS

ALPROLIX is contraindicated in patients who have manifested severe hypersensitivity reactions, including anaphylaxis, to the product or its components. Severe hypersensitivity reactions were not observed in clinical trials; however, these have been known to occur with use of other factor IX replacement factors.

PRECAUTIONS

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 PRECAUTIONS - Monitoring Laboratory Tests)*.

Anaphylaxis and Severe Hypersensitivity Reactions
Allergic type hypersensitivity reactions, including anaphylaxis, are possible with factor replacement therapies. The presence of inhibitors has been associated with allergic reactions with other factor IX replacement therapies. 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 DOSAGE AND ADMINISTRATION)*.

Neutralising Antibodies (Inhibitors)
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 factor replacement therapy in the treatment of Haemophilia B. 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 PRECAUTIONS - 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 DOSAGE AND 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).

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. 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.

Paediatric use

Safety, efficacy, and pharmacokinetics of ALPROLIX have been evaluated in previously treated paediatric patients ages 12 years and older. No dose adjustment is required.

No data are available for patients below the age of 12 years.

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 DOSAGE AND ADMINISTRATION)*.

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.

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).

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

The most common adverse reactions observed in the multi-center, open label, prospective study (incidence ≥1%) for ALPROLIX were headache and oral paraesthesia.

A serious adverse reaction of obstructive uropathy was reported in a subject with haematuria who developed an obstructing clot in the urinary collecting system. The event resolved with hydration and the subject continued prophylactic treatment with ALPROLIX.

In the multi-centre, open-label prospective clinical study with ALPROLIX, 123 previously treated patients (PTPs) were evaluated, with 115 subjects treated at least 26 weeks and 56 subjects treated for at least 52 weeks. Adverse drug reactions (ADRs) were reported in 10 of 119 (8.4%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. Adverse drug reactions are considered adverse events assessed by the investigator as related or possibly related to treatment with ALPROLIX. Adverse drug reactions are summarised in Table 9. No subject was withdrawn from study due to an adverse drug reaction. In the study, no inhibitors were detected and no events of anaphylaxis were reported.

Table 9: Adverse Drug Reactions reported for ALPROLIX

MedDRA System Organ Class	MedDRA Preferred Term	N=119* Number of Subjects N (%)	Frequency Category
Nervous system disorders	Headache Dizziness Dysgeusia	2 (1.7) 1 (0.8) 1 (0.8)	Common Uncommon Uncommon
Gastrointestinal disorders	Paresthesia oral Breath odor	2 (1.7) 1 (0.8)	Common Uncommon
General disorders and administration site conditions	Fatigue Infusion site pain	1 (0.8) 1 (0.8)	Uncommon Uncommon
Cardiac disorders	Palpitations	1 (0.8)	Uncommon
Renal and urinary disorders	Obstructive uropathy	1 (0.8)	Uncommon
Vascular disorders	Hypotension	1 (0.8)	Uncommon

Legend: 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)
*119 previously treated patients (PTPs) on routine prophylaxis or episodic (on-demand) therapy

DOSAGE AND ADMINISTRATION

For Intravenous Use Only After Reconstitution.

Treatment with ALPROLIX should be initiated under the supervision of a qualified healthcare professional experienced in the treatment of haemophilia B. 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.

Careful control of replacement therapy is especially important in cases of life-threatening bleeding episodes or major surgery *(see Table 10 and Table 11).*

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 PRECAUTIONS and PHARMACOLOGY - Pharmacokinetics).*

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 1% [IU/dL].

ALPROLIX has been shown to have a prolonged circulating half-life. No dose adjustment for recovery is generally required. 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
The following table can be used to guide dosing in bleeding episodes:

Table 10: 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	**80-120**	**100 IU/kg** For repeat dosing, follow guidelines for major surgery (*see* Table 11)

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

Subsequent dosage and duration of treatment depends on the individual clinical response, the severity of the factor IX deficiency, and the location and extent of bleeding *(see PHARMACOLOGY - Pharmacokinetics).*

Perioperative Management

The following table can be used to guide dosing for and perioperative management (surgical prophylaxis):

Table 11: 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 120 (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
* *see PHARMACOLOGY - Pharmacokinetics*

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 PHARMACOLOGY - Pharmacokinetics).*

Effect of Food

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

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.

Effects on Ability to Drive and Use Machines

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

OVERDOSAGE

No symptoms of overdose have been reported. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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 5 vial sizes - 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU. Actual factor IX activity in International Units is stated on the label of each ALPROLIX carton and vial.

Protect from light. Unopened vials should be stored under controlled refrigeration (2°C - 8°C). 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.

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.

Dispose of all the materials in accordance with local requirements.

NAME AND ADDRESS OF THE SPONSOR

Biogen Idec Australia Pty Ltd
ABN 30 095 760 115
Suite 1, Level 5, 123 Epping Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION ON THE ARTG

1 May 2014

ALPROLIX® (all-pro-liks)

Eftrenonacog alfa (rhu)

Recombinant coagulation factor IX Fc fusion protein 250, 500, 1000, 2000, 3000 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 4 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

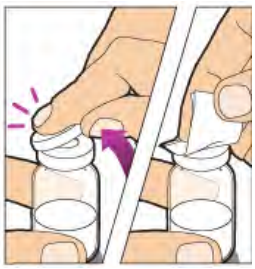
A1. First ensure that your work area is clean.

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.

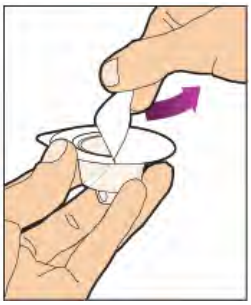
A3. Wash your hands thoroughly with soap and water before performing the following procedures.

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.

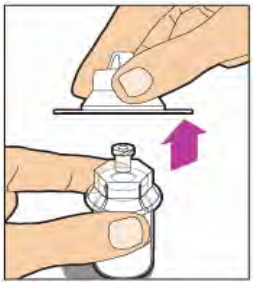


A6. Completely remove the backing from the vial adapter package by peeling back the lid. **Do not remove the vial adapter from the package or touch the inside of the package or the adapter.**



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.

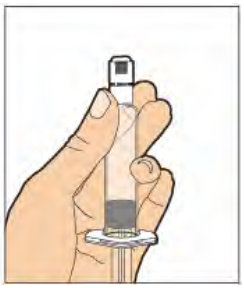
A8. Lift the package cover away from the vial adapter and discard the cover.



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.**



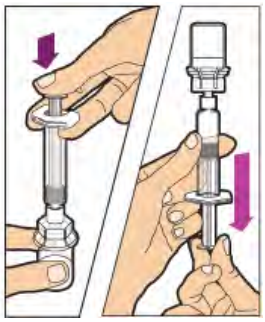
B2. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe**. Do not touch the glass tip of the syringe or the inside of the cap.**

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.

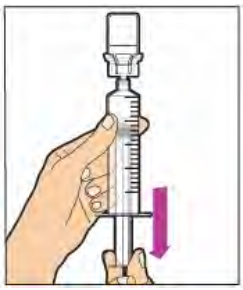
C1. Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a large luer lock syringe.

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.

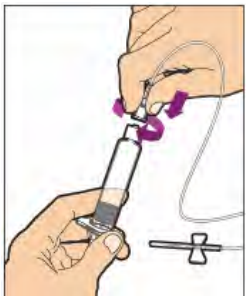


D. Giving the injection

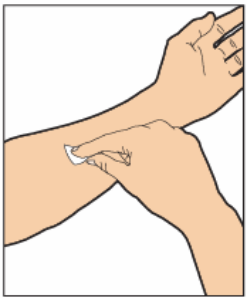
For Intravenous Use only after Reconstitution
ALPROLIX is administered by intravenous (IV) infusion after reconstitution of the drug powder with the diluent.

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

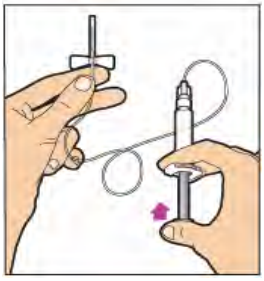
D1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. **Do not administer reconstituted ALPROLIX in the same tubing or container with other medicinal products. Do not remove the protective needle cover until you are ready to insert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



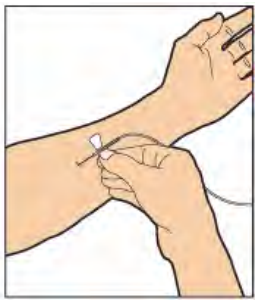
D2. Apply a tourniquet and clean the skin area where you will perform the infusion using an alcohol wipe.



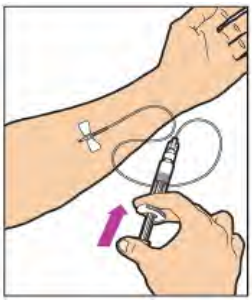
D3. Depress the plunger until all air is removed from the syringe and ALPROLIX has reached the end of the infusion set tubing. Do not push ALPROLIX through the needle.



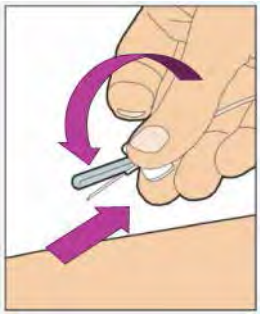
D4. Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



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.



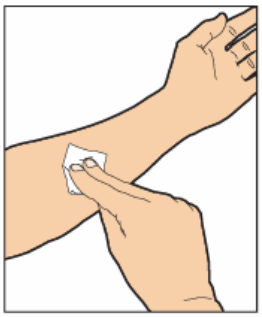
D6. After infusing ALPROLIX, flip the safety shield towards the needle. Remove the infusion set.



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.