SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALPROLIX 250 IU powder and solvent for solution for injection

ALPROLIX 500 IU powder and solvent for solution for injection

ALPROLIX 1000 IU powder and solvent for solution for injection

ALPROLIX 2000 IU powder and solvent for solution for injection

ALPROLIX 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALPROLIX 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU human coagulation factor IX (rDNA), eftrenonacog alfa. ALPROLIX contains approximately 250 IU (50 IU/mL) of human coagulation factor IX (rDNA), eftrenonacog alfa after reconstitution.

ALPROLIX 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU human coagulation factor IX (rDNA), eftrenonacog alfa. ALPROLIX contains approximately 500 IU (100 IU/mL) of human coagulation factor IX (rDNA), eftrenonacog alfa after reconstitution.

ALPROLIX 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU human coagulation factor IX (rDNA), eftrenonacog alfa. ALPROLIX contains approximately 1000 IU (200 IU/mL) of human coagulation factor IX (rDNA), eftrenonacog alfa after reconstitution.

ALPROLIX 2000 IU powder and solvent for solution for injection
Each vial contains nominally 2000 IU human coagulation factor IX (rDNA), eftrenonacog alfa. ALPROLIX contains approximately 2000 IU (400 IU/mL) of human coagulation factor IX (rDNA), eftrenonacog alfa after reconstitution.

ALPROLIX 3000 IU powder and solvent for solution for injection
Each vial contains nominally 3000 IU human coagulation factor IX (rDNA), eftrenonacog alfa. ALPROLIX contains approximately 3000 IU (600 IU/mL) of human coagulation factor IX (rDNA), eftrenonacog alfa after reconstitution.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of ALPROLIX is 55-84 IU/mg protein.

Eftrenonacog alfa (recombinant human coagulation factor IX, Fc fusion protein (rFIXFc)) has 867 amino acids. It is a high purity factor product produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, without the addition of any exogenous human- or animal-derived protein in the cell culture, purification or final formulation.

Excipient with known effect
0.3 mmol (6.4 mg) sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Powder: lyophilised, white to off-white powder or cake.
Solvent: clear to colourless solution.

pH: 6.5 to 7.5
Osmolality: 255 to 345 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

ALPROLIX can be used for all age groups.
Treatment monitoring
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated injections. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.

When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay.
Measurements with a one-stage clotting assay utilising a kaolin-based aPTT reagent will likely result in an underestimation of activity level.

Posology
Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

One International Unit (IU) of recombinant factor IX Fc activity is equivalent to that quantity of factor IX in one mL of normal human plasma.

On demand treatment
The calculation of the required dose of recombinant factor IX Fc is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1 % of normal activity (IU/dL). The required dose is determined using the following formula:

Required units = body weight (kg) × desired factor IX rise (%) (IU/dL) × {reciprocal of observed recovery (IU/kg per IU/dL)}

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. If a repeat dose is required to control the bleed, the prolonged half-life of ALPROLIX should be taken into account (see section 5.2). The time to peak activity is not expected to be delayed.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. Table 1 can be used to guide dosing in bleeding episodes and surgery:

Table 1: Guide to ALPROLIX dosing for treatment of bleeding episodes and surgery

Degree of haemorrhage / Type of surgical procedure	**Factor IX level required (%) (IU/dL)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat injection every 48 hours, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat injection every 24 to 48 hours until pain and acute disability are resolved.
Life threatening haemorrhages	60-100	Repeat injection every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30-60	Repeat injection after 24 hours, as needed until healing is achieved[1].
Major surgery	80-100 (pre- and post-operative)	Repeat injection every 8 to 24 hours as necessary until adequate wound healing, then therapy at least for another 7 days to maintain a factor IX activity of 30% to 60% (IU/dL).

[1] In some patients and circumstances the dosing interval can be prolonged up to 48 hours (see section 5.2 for pharmacokinetic data).

Prophylaxis
For long term prophylaxis against bleeding, the recommended starting regimens are either:

- 50 IU/kg once weekly, adjust dose based on individual response or
- 100 IU/kg once every 10 days, adjust interval based on individual response. Some patients who are well-controlled on a once every 10 days regimen might be treated on an interval of 14 days or longer.

The highest recommended dose for prophylaxis is 100 IU/kg

Elderly population
There is limited experience in patients ≥65 years.

Paediatric population
For children below the age of 12 years, higher or more frequent doses may be required, and the recommended starting dose is 50-60 IU/kg every 7 days. For adolescents of 12 years of age and above, the dose recommendations are the same as for adults. See sections 5.1 and 5.2.
The highest recommended dose for prophylaxis is 100 IU/kg

Method of administration
Intravenous use.

In case of self-administration or administration by a caregiver appropriate training is needed.

ALPROLIX should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level and should not exceed 10 mL/min.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions have been reported with ALPROLIX. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including, hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of anaphylactic shock, standard medical treatment for shock should be implemented.

Inhibitors
After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Thromboembolism
Because of the potential risk of thrombotic complications with factor IX products, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or disseminated intravascular coagulation (DIC). The benefit of treatment with ALPROLIX in these situations should be weighed against the risk of these complications.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with factor IX products may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Excipient related considerations
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free". In case of treatment with multiple vials, the total sodium content should be taken into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of ALPROLIX with other medicinal products have been reported. No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
Animal reproduction studies have not been conducted with ALPROLIX. A placental transfer study in mice was conducted (see section 5.3). Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available. No fertility studies have been conducted in animals with ALPROLIX.

4.7 Effects on ability to drive and use machines

ALPROLIX has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with thromboembolic complications.

Tabulated list of adverse reactions
Previously Treated Patients (PTPs): A total of 153 patients with severe haemophilia B were observed in phase III clinical studies and an extension study. Adverse events were monitored for a total of 561 subject-years. The total number of exposure days was 26,106 with a median of 165 (range 1 to 528) exposure days per subject.

Previously Untreated Patients (PUPs): A total of 33 patients with severe haemophilia B were observed in one clinical study. Adverse events were monitored for a total of 57.51 subject-years. The total number of exposure days was 2,233 with a median of 76 (range 1 to 137) exposure days per subject.

Table 2 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). The table lists adverse reactions reported in the clinical studies and identified in post-marketing use.

Table 2: Adverse reactions reported for ALPROLIX

MedDRA System Organ Class	**Adverse reactions**	**Frequency category**
Blood and lymphatic system disorders	Factor IX inhibition	Common[1]
Immune system disorders	Hypersensitivity	Common[1]
	Anaphylactic reaction	Not known
	Anaphylactic shock	Not known
Metabolism and nutrition disorders	Decreased appetite	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
	Dysgeusia	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Hypotension	Uncommon
Gastrointestinal disorders	Paraesthesia oral	Common
	Breath odour	Uncommon
Renal and urinary disorders	Obstructive uropathy	Common
	Haematuria	Uncommon
	Renal colic	Uncommon
General disorders and administration site conditions	Injection site erythema	Common
	Fatigue	Uncommon
	Infusion site pain	Uncommon

[1] Frequency based on occurrence in PUPs study. Both events of factor IX inhibition and hypersensitivity occurred in a single PUP in Study IV. See Description of selected adverse reactions.

Description of selected adverse reactions

Throughout the clinical study program, one patient (previously untreated) in Study IV developed a low titer factor IX inhibitor associated with hypersensitivity (see section 5.1). In post-marketing experience, factor IX inhibitor development and hypersensitivity (including anaphylaxis) have been observed.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be similar as in adults. For extent and age characterisation of the safety database in children see section 5.1.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

The effects of higher than recommended doses of ALPROLIX have not been characterised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor IX, ATC code: B02BD04

Mechanism of action
Factor IX is a single chain glycoprotein with a molecular mass of about 55,000 Dalton. It is a vitamin-K dependent coagulation factor. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.
Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma level of factor IX is increased thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

ALPROLIX (eftrenonacog alfa) is a long-acting, fully recombinant, fusion protein comprising human coagulation factor IX covalently linked to the Fc domain of human immunoglobulin G1, and produced by recombinant DNA technology.

The Fc region of human immunoglobulin G1 binds with the neonatal Fc receptor. 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.

Clinical efficacy and safety
The safety, efficacy, and pharmacokinetics of ALPROLIX were evaluated in 2 multinational, open-label, pivotal studies in previously treated patients (PTPs); a phase 3 study in adults and adolescents, referred to as Study I and a phase 3 paediatric study, referred to as Study II (see Paediatric population). The safety and efficacy of ALPROLIX was also evaluated in previously untreated patients (PUPs) with severe haemophilia B (Study IV), see Paediatric population.

Study I compared the efficacy of each of 2 prophylactic treatment regimens (fixed weekly interval with dosing of 50 IU/kg, and individualised interval with 100 IU/kg starting every 10 days) to on demand treatment. The study enrolled a total of 123 previously treated male patients (12 to 71 years of age) with severe haemophilia B (≤2% endogenous FIX activity). All patients received treatment with ALPROLIX and were followed for up to 77 weeks.

Out of 123 subjects who completed Study I, 93 were enrolled in Study III (extension study) with median total follow-up time of 6.5 years.

Of note, Annualised Bleeding Rates (ABR) are not comparable between different factor concentrates and between different clinical studies.

Prophylaxis fixed weekly and individualised intervals
Median weekly dose for subjects in the fixed weekly arm was 45.17 IU/kg (interquartile range (IQR) 38.1 - 53.7) in Study I. The corresponding median ABR in subjects evaluable for efficacy were 2.95 (IQR: 1.01-4.35) and remained similar throughout Study III (1.85 (IQR: 0.76-4.0)). Subjects had a median of 0.38 (IQR: 0.00-1.43) spontaneous joint bleeds in Study III.

For subjects in the individualised interval arm, the median dosing interval was 12.53 days (IQR: 10.4-13.4) in Study I. The corresponding median ABR was 1.38 (IQR: 0.00-3.43) and remained similar throughout Study III (1.85 (IQR: 0.76-4.0)).

Dosing intervals and factor consumption remained similar in Study III (extension study) compared to Study I for both prophylactic regimens.

No bleeding episodes were experienced in 42% of subjects while on individualised prophylaxis and in 23% of subjects while on weekly prophylaxis. There was a lower proportion of subjects in individualised interval prophylaxis with ≥1 target joint at baseline than in weekly prophylaxis (27.6% and 57.1%, respectively).

Treatment of bleeding
Of the 636 bleeding events observed during Study I, 90.4% were controlled with 1 injection and overall 97.3% with 2 or fewer injections. The median average dose per injection to treat a bleeding episode was 46.07 (IQR: 32.86-57.03) IU/kg. The median overall dose to treat a bleeding episode was 51.47 IU/kg (IQR: 35.21-61.73) in the weekly prophylaxis arm, 49.62 IU/kg (IQR: 35.71-94.82) in the individualised interval prophylaxis arm and 46.58 IU/kg (IQR: 33. 33-59.41) in the on-demand treatment arm.

Perioperative management (surgical prophylaxis)
A total of 35 major surgical procedures were performed and assessed in 22 subjects (21 adults and adolescents, and 1 paediatric patient <12 years of age) in Study I and Study III. 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 IU/kg). The total dose on the day of surgery ranged from 49 to 341 IU/kg and the total dose in the 14-day perioperative period ranged from 60 to 1947 IU/kg.

The haemostatic response was rated as excellent or good in 100% of major surgeries.

Paediatric population

Study II enrolled a total of 30 previously treated male paediatric patients with severe haemophilia B (≤2% endogenous FIX activity). Patients were less than 12 years of age (15 were <6 years of age and 15 were 6 to <12 years of age). All patients received treatment with ALPROLIX and were followed for up to 52 weeks.

All of the 30 patients were treated with ALPROLIX on a prophylactic dosing 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. Out of 30 patients having completed Study II, 27 enrolled to Study III (extension study). The median time on Study II+III was 2.88 years and median number of exposure days was 166.

Study IV enrolled 33 previously untreated paediatric patients (PUPs) with severe haemophilia B (≤2% endogenous FIX activity). The median age at enrolment was 0.6 years (range 0.08 to 2 years); 78.8% of subjects were less than 1 year old. The overall median number of weeks on ALPROLIX was 83.01 (range 6.7 to 226.7 weeks), and the overall median number of EDs was 76 days (range 1 to 137 days).

Prophylaxis individualised regimen
In Study II the median average weekly dose of ALPROLIX was 59.40 IU/kg (interquartile range, 52.95 to 64.78 IU/kg) for subjects <6 years of age and 57.78 IU/kg (interquartile range, 51.67 to 65.01 IU/kg) for subjects 6 to <12 years of age. The median dosing interval overall was 6.99 days (interquartile range, 6.94 to 7.03) with no difference in the median dosing interval between age cohorts. With the exception of one patient whose last prescribed dose was 100 IU/kg every 5 days, the other 29 patients last prescribed doses were up to 70 IU/kg every 7 days. No bleeding episodes were experienced in 33% of paediatric subjects. Dosing intervals and factor consumption remained similar in Study III compared to Study II.

Median annualised bleeding rates in subjects <12 years of age evaluable for efficacy were 1.97 (interquartile range 0.00 to 3.13) in Study II and remained similar throughout Study III (extension study).

In PUPs (Study IV) the median average weekly dose of ALPROLIX was 57.96 IU/kg (interquartile range 52.45 to 65.06 IU/kg) and the median average dosing interval was 7 days (interquartile range 6.95 to 7.12 days). Dosing intervals and factor consumption remained similar in Study IV compared to Study II and III. For PUPs receiving prophylactic treatment, 8 (28.6 %) of the subjects experienced no bleeding episodes. The overall median ABR for subjects in the prophylactic treatment regimen was 1.24 (interquartile range 0.0 to 2.49).

Treatment of bleeding episodes

Of the 60 bleeding events observed during Study II, 75% were controlled with 1 injection, and overall 91.7% of bleeding episodes were controlled with 2 or fewer injections. The median average dose per injection to treat a bleeding episode was 63.51 (interquartile range, 48.92 to 99.44) IU/kg. The median overall dose to treat a bleeding episode was 68.22 IU/kg (interquartile range, 50.89 to 126.19).

Of the 58 bleeding events observed in PUPs receiving prophylactic treatment in Study IV, 87.9% were controlled with 1 injection, and overall 96.6% of bleeding episodes were controlled with 2 or fewer injections. The median average dose per injection to treat a bleeding episode was 71.92 IU/kg (interquartile range 52.45 to 100.81 IU/kg). The median overall dose to treat a bleeding episode was 78.74 IU/kg (interquartile range 53.57 to 104.90 IU/kg).

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ALPROLIX were conducted in previously treated patients with severe haemophilia B. Data presented in this section were obtained by one-stage clotting assay with a silica-based aPTT reagent calibrated against factor IX plasma standards.

Pharmacokinetic properties were evaluated in 22 subjects (≥19 years) receiving ALPROLIX (rFIXFc). Following a washout period of at least 120 hours (5 days), the subjects received a single dose of 50 IU/kg. Pharmacokinetic samples were collected pre-dose and then subsequently at 11 time points up to 240 hours (10 days) post-dose. Pharmacokinetic parameters of the non-compartmental analysis after 50 IU/kg dose of ALPROLIX are presented in Table 3.

Table 3: Pharmacokinetic parameters of ALPROLIX (50 IU/kg dose)

Pharmacokinetic parameters[1]	**ALPROLIX (95% CI)**
	N=22
Incremental Recovery (IU/dL per IU/kg)	0.92 (0.77-1.10)
AUC/Dose (IU*h/dL per IU/kg)	31.58 (28.46-35.05)
C_{max} (IU/dL)	46.10 (38.56-55.11)
CL (mL/h/kg)	3.17 (2.85-3.51)
$t_{½}$ (h)	77.60 (70.05-85.95)
$t_{½\alpha}$ (h)[2]	5.03 (3.20-7.89)
$t_{½\beta}$ (h)[2]	82.12 (71.39-94.46)
MRT (h)	95.82 (88.44-106.21)
V_{ss} (mL/kg)	303.4 (275.1-334.6)
Time to 1% (days)[2]	11.22 (10.20-12.35)

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

[2] These pharmacokinetic parameters obtained from the compartmental analysis

Abbreviations: CI = confidence interval; C_{max}= maximum activity; AUC = area under the FIX activity time curve; $t_{1/2}$ = terminal half-life; $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$ = elimination half-life; CL = clearance; Vss = volume of distribution at steady-state; MRT = mean residence time.

The elimination half-life (82 hours) is influenced by the Fc region, which in animal models was shown to be mediated by neonatal Fc receptor cycling pathways.

A population pharmacokinetic model was developed based on FIX activity data from 161 subjects of all ages (2-76 years of age) weighing between 12.5 kg to 186.7 kg in three clinical studies (12 subjects in a phase 1/2a study, 123 subjects in Study I and 26 subjects in Study II). The estimate of CL for a typical 70 kg

adult is 2.30 dL/h and steady-state volume of distribution is 194.8 dL, respectively. The observed mean (SD) activity time profile following a single dose of ALPROLIX in patients with severe haemophilia B is shown below (see Table 4).

Table 4: The Observed Mean (SD) FIX activity [IU/dL] following a single dose of ALPROLIX[1] (rFIXFc) for patients ≥ 12 years of Age

Dose (IU/kg)	10 mins	1h	3h	6h	24h	48h	96h	144h	168h	192h	240h	288h
50	52.9 (30.6)	34.5 (7.3)	28.7 (6.7)	25.1 (5.1)	15.1 (3.9)	9.7 (3.0)	5.0 (1.6)	3.4 (1.1)	3.2 (1.9)	2.6 (1.0)	2.1 (0.9)	NA
100	112 (24)	NA	77.1 (12.8)	NA	36.7 (8.0)	21.8 (4.8)	10.1 (2.6)	NA	4.81 (1.67)	NA	2.86 (0.98)	2.30 (0.94)

[1] See section 4.2; NA: Not available

Paediatric population

Pharmacokinetic parameters of ALPROLIX were determined for adolescents in Study I (pharmacokinetic sampling was conducted pre-dose followed by assessment at multiple time points up to 336 hours (14 days) post-dose) and for children in Study II (pharmacokinetic sampling was conducted pre-dose followed by assessment at 7 time points up to 168 hours (7 days) post-dose). Table 5 presents the pharmacokinetic parameters calculated from the paediatric data of 35 subjects less than 18 years of age.

Table 5: Comparison of PK Parameters of ALPROLIX (rFIXFc) by Age Category

PK Parameters[1]	Study II		Study I
	<6 years (2, 4)	**6 to <12 years (6, 10)**	**12 to <18 years (12, 17)**
	N = 11	**N = 13**	**N = 11**
IR (IU/dL per IU/kg)	0.5989 (0.5152, 0.6752)	0.7170 (0.6115, 0.8407)	0.8470 (0.6767, 1.0600)
AUC/Dose (IU*h/dL per IU/kg)	22.71 (20.32, 25.38)	28.53 (24.47, 33.27)	29.50 (25.13, 34.63)
$t_{½}$ (h)	66.49 (55.86, 79.14)	70.34 (60.95, 81.17)	82.22 (72.30, 93.50)
MRT (h)	83.65 (71.76, 97.51)	82.46 (72.65, 93.60)	93.46 (81.77, 106.81)
CL (mL/h/kg)	4.365 (3.901, 4.885)	3.505 (3.006, 4.087)	3.390 (2.888, 3.979)
V_{SS} (mL/kg)	365.1 (316.2, 421.6)	289.0 (236.7, 352.9)	316.8 (267.4, 375.5)

[1]PK parameters derived from noncompartmental analysis are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; IR = incremental recovery; AUC = area under the FIX activity time curve; $t_{1/2}$ = terminal half-life; MRT = mean residence time; CL = clearance; Vss = volume of distribution at steady-state

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on thrombogenicity test in rabbits (Wessler stasis model) and repeated dose toxicity studies (which included assessment of local toxicity, male reproductive organs and electrocardiographic parameters) in rats and monkeys. Studies to investigate genotoxicity, carcinogenicity, toxicity to reproduction or embryo-foetal development have not been conducted. In a placental transfer study, eftrenonacog alfa (rFIXFc) has been shown to cross the placenta in small amounts in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol
Sucrose
Histidine

Polysorbate 20
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

Solvent
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Only the provided infusion set should be used because treatment failure can occur as a consequence of coagulation factor IX adsorption to the internal surfaces of some injection equipment.

6.3 Shelf life

Unopened vial
The expiry date of the product is indicated on the packaging materials
During the shelf-life, the product may be stored at room temperature (up to 30 °C) for a single period not exceeding 6 months. The date that the product is removed from refrigeration should be recorded on the carton. After storage at room temperature, the product may not be returned to the refrigerator. The product should not be used beyond the expiry date printed on the vial or six months after removing the carton from refrigeration, whichever is earlier.

After reconstitution
Chemical and physical stability has been demonstrated for 6 hours when stored at room temperature (up to 30 °C). If the product is not used within 6 hours, it must be discarded. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Protect product from direct sunlight.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration

Each pack contains:
- powder in a type 1 glass vial with a chlorobutyl rubber stopper
- 5 mL solvent in a type 1 glass pre-filled syringe with a bromobutyl rubber plunger stopper
- a plunger rod
- a sterile vial adapter for reconstitution
- a sterile infusion set
- alcohol swab(s)

- plaster(s)
- gauze pad(s).

Pack size of 1.

6.6 Special precautions for disposal and other handling

The powder for injection in each vial must be reconstituted with the supplied solvent (sodium chloride solution) from the pre-filled syringe using the sterile vial adapter for reconstitution.

The vial should be gently swirled until all of the powder is dissolved.

The reconstituted solution should be clear to slightly opalescent and colourless. Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.

This product is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for preparation and administration

The procedure below describes the preparation and administration of ALPROLIX.

ALPROLIX is administered by intravenous (IV) injection after dissolving the powder for injection with the solvent supplied in the pre-filled syringe. ALPROLIX pack contains:

A) 1 Powder vial
B) 5 mL Solvent in pre-filled syringe
C) 1 Plunger rod
D) 1 Vial adapter
E) 1 Infusion set
F) 2 Alcohol swabs
G) 2 Plasters
H) 1 Gauze pad

ALPROLIX should not be mixed with other solutions for injection or infusion.

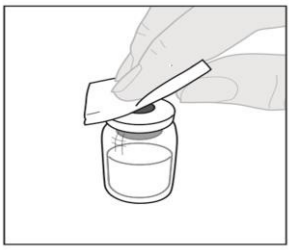
Wash your hands before opening the pack.

Preparation:

1.	Check the name and strength of the package, to make sure it contains the correct medicine. Check the expiry date on the ALPROLIX carton. Do not use if the product has expired.
2.	If ALPROLIX has been stored in a refrigerator, allow the vial of ALPROLIX (A) and the syringe with solvent (B) to reach room temperature before use. Do not use external heat.

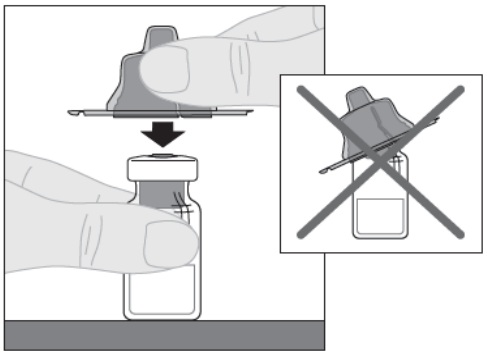
3. Place the vial on a clean flat surface. Remove the plastic flip-top cap from the vial.

4. Wipe the top of the vial with one of the alcohol swabs (F) provided in the pack and allow to air dry. Do not touch the top of the vial or allow it to touch anything else once wiped.

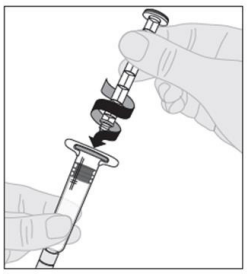


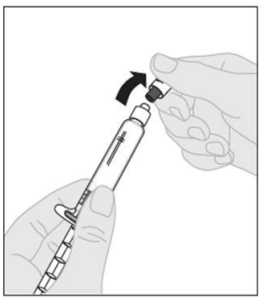
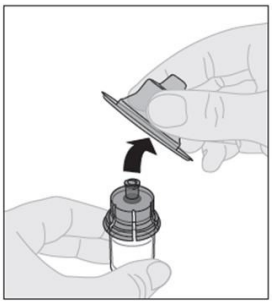
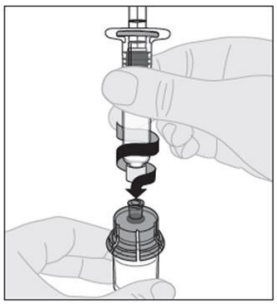
5. Peel back the protective paper lid from the clear plastic vial adapter (D). Do not remove the adapter from its protective cap. Do not touch the inside of the vial adapter package.

6. Place the vial on a flat surface. Hold the vial adapter in its protective cap and place it squarely over the top of the vial. Press down firmly until the adapter snaps into place on top of the vial, with the adapter spike penetrating the vial stopper.

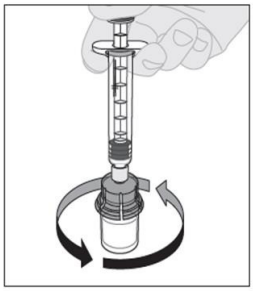


7. Attach the plunger rod (C) to the solvent syringe by inserting the tip of the plunger rod into the opening in the syringe plunger. Turn the plunger rod firmly clockwise until it is securely seated in the syringe plunger.



8.	Break off the white, tamper-resistant, plastic cap from the solvent syringe by bending the perforation cap until it snaps off. Set the cap aside by placing it with the top down on a flat surface. Do not touch the inside of the cap or the syringe tip.	
9.	Lift the protective cap away from the adapter and discard.	
10.	Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening. Firmly push and turn the syringe clockwise until it is securely connected.	
11.	Slowly depress the plunger rod to inject all the solvent into the ALPROLIX vial.	

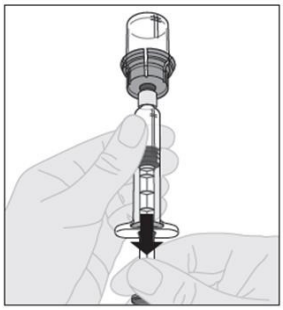
12. With the syringe still connected to the adapter and the plunger rod pressed down, gently swirl the vial until the powder is dissolved.
Do not shake.



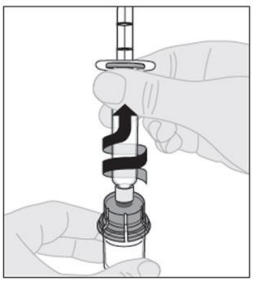
13. The final solution must be inspected visually before administration. The solution should appear clear to slightly opalescent (pearl-like) and colourless. Do not use the solution if cloudy or contains visible particles.

14. Ensuring that the syringe plunger rod is still fully pressed down, invert the vial. Slowly pull on the plunger rod to draw back all the solution through the vial adapter into the syringe.

Note: If you use more than one vial of ALPROLIX per injection, each vial should be prepared separately as per the previous instructions (steps 1 to 13) and the solvent syringe should be removed, leaving the vial adapter in place. A single large luer lock syringe may be used to draw back the prepared contents of each of the individual vials.



15. Detach the syringe from the vial adapter by gently pulling and turning the vial counterclockwise.



16. Discard the vial and the adapter.

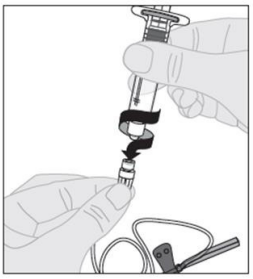
Note: If the solution is not to be used immediately, the syringe cap should be carefully put back on the syringe tip. Do not touch the syringe tip or the inside of the cap.

After preparation, ALPROLIX can be stored at room temperature for up to 6 hours before administration. After this time, the prepared ALPROLIX should be discarded. Protect from direct sunlight.

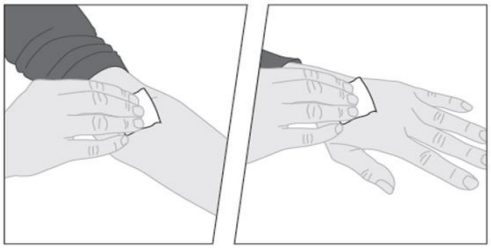
Administration (Intravenous Injection):

ALPROLIX should be administered using the infusion set (E) provided in this pack.

1. Open the infusion set package and remove the cap at the end of the tubing. Attach the syringe with the prepared ALPROLIX solution to the end of the infusion set tubing by turning clockwise.



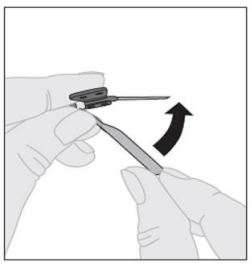
2. If needed apply a tourniquet and prepare the injection site by wiping the skin well with the other alcohol swab provided in the pack.



3. Remove any air in the infusion set tubing by slowly depressing on the plunger rod until liquid has reached the infusion set needle. Do not push the solution through the needle. Remove the clear plastic protective cover from the needle.

4. Insert the infusion set needle into a vein as instructed by your doctor or nurse and remove the tourniquet. If preferred, you may use one of the plasters (G) provided in the pack to hold the plastic wings of the needle in place at the injection site. The prepared product should be injected intravenously over several minutes. Your doctor may change your recommended injection rate to make it more comfortable for you.

5. After completing the injection and removing the needle, you should fold over the needle protector and snap it over the needle.



6. Please safely dispose of the used needle, any unused solution, the syringe and the empty vial in an appropriate medical waste container as these materials may hurt others if not disposed of properly. Do

not reuse equipment.

7. MANUFACTURER:

Swedish Orphan Biovitrum AB (publ)
Strandbergsgatan 49, 11 276 Stockholm
Sweden

8. License Holder:

Megapharm Ltd
HATIDHAR ST. 15, RA'ANANA, 4366517, ISRAEL

9. MARKETING AUTHORISATION NUMBER(S)

Alprolix 250 IU	171-47-37091-00
Alprolix 500 IU	171-48-36890-00
Alprolix 1000 IU	171-49-36891-00
Alprolix 2000 IU	171-50-36892-00
Alprolix 3000 IU	171-51-36893-00

10. Revised in May 2024 according to MOHs guidelines.

ALPSPC 052024 P.1