ALPROLIX®
[Coagulation Factor IX (Recombinant), Fc Fusion Protein]

Dosing Overview

Clinical trial experience with extended dosing

INDICATIONS:

ALPROLIX® is a recombinant DNA derived, coagulation Factor IX concentrate indicated in adults and children with hemophilia B for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of Use

ALPROLIX is not indicated for induction of immune tolerance in patients with hemophilia B.

CONTRAINDICATIONS:

ALPROLIX is contraindicated in patients who have a known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients.

Please see Important Safety Information on last page and Full Prescribing Information.

How to initiate therapy with ALPROLIX® prophylaxis[1]

For adults and adolescents, the recommended starting dose is

50 IU/kg every 7 days

- ALPROLIX may also be initiated at 100 IU/kg every 10 days

For children aged <12 years, the recommended starting dose is

60 IU/kg once weekly

with adjustments made based on patient response

- More frequent or higher doses may be needed in children aged <12 years, especially in children aged <6 years
- On average, 1 IU/kg of ALPROLIX per kg of body weight increases the level of circulating factor IX by approximately 1.0% in children aged ≥6 years and 0.6% in children aged <6 years

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Extended dosing intervals with ALPROLIX prophylaxis[1]

For adult patients currently on ALPROLIX 50 IU/kg every 7 days, it is recommended to:

Double the dose and increase the interval to

100 IU/kg every 10 days

In clinical trials, some patients were able to increase their interval to

100 IU/kg every 14 days

Extension of the recommended dosing regimen should be based on individual response.

Important Safety Information

- Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with factor replacement therapies, and have been reported with ALPROLIX. Discontinue use of ALPROLIX if hypersensitivity symptoms occur, and initiate appropriate treatment.

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The safety and efficacy of ALPROLIX® were demonstrated in the B-LONG trial[1,2]

B-LONG was a phase 3 study of ALPROLIX in 123 patients with severe hemophilia B

- Studied previously treated males aged ≥12 years with severe hemophilia B (≤2 IU of endogenous factor IX per deciliter)
- Patients were studied for up to 77 weeks

In the B-LONG trial, patients were assigned to 1 of 4 treatment arms:

Prestudy prophylactic or episodic treatment	→ Arm 1	**Fixed-interval (weekly) prophylaxis** 50 IU/kg every 7 days, with the dose adjusted to maintain factor levels 1 to 3 IU/dL above baseline or higher if clinically indicated	n=63
	→ Arm 2	**Fixed-dose (interval-adjusted) prophylaxis** 100 IU/kg every 10 days, with the interval adjusted to maintain factor levels 1 to 3 IU/dL above baseline or higher if clinically indicated[a]	n=29
Prestudy episodic treatment	→ Arm 3	**On-demand (episodic) treatment** 20 to 100 IU/kg as required	n=27
	Arm 4	**Perioperative treatment** 40 to 100 IU/kg as required	n=12[b]

[a]Adjustments to the initial 10-day interval were to be made based on baseline pharmacokinetic (PK) assessments and trough levels, which were monitored at Weeks 4, 16, 26, and 39.[3]

[b]Arm 4 included 2 patients who moved to Arm 1 and 6 patients who moved from Arm 1 or Arm 3.

Postmarketing safety experience with ALPROLIX[1]

- Formation of inhibitors to factor IX has been reported following an administration of ALPROLIX in postmarketing experience, including in previously untreated patients
- The use of factor IX products has been associated with the development of thromboembolic complications, especially in individuals receiving continuous infusion through a central venous catheter
- Hypersensitivity reactions have been reported with ALPROLIX in postmarketing experience

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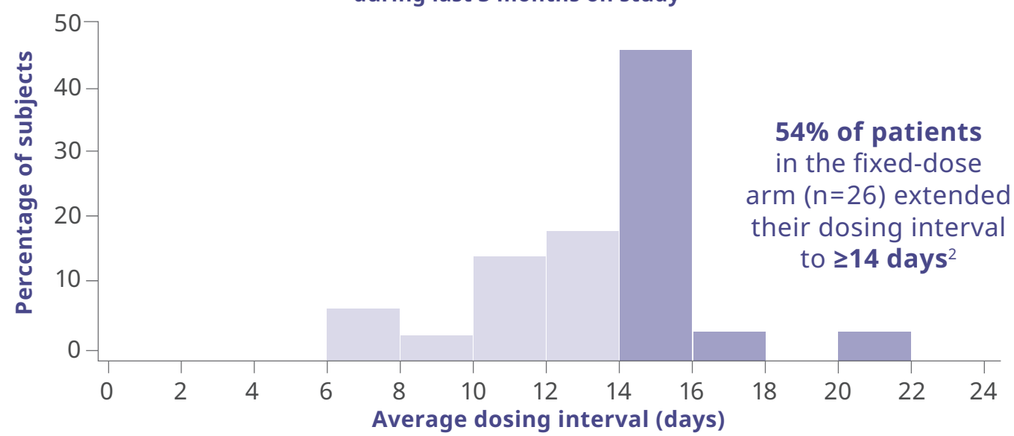
Some adult and adolescent patients achieved extended dosing intervals[1-3]

In the B-LONG trial, some patients from the fixed-dose arm were able to achieve a ≥14-day dosing interval

- Patients in the fixed-dose arm were initially treated with 100 IU/kg of ALPROLIX every 10 days and worked with their health care provider to determine whether extending their interval was appropriate
- The dose was maintained at 100 IU/kg and the interval was adjusted based on the following:
  - — Baseline pharmacokinetic assessments and trough levels of 1% to 3% or higher
  - — Either <2 spontaneous bleeding episodes over a rolling 3-month period or factor IX trough levels of 3% to 5% above baseline, or the investigator's discretion
  - — Adjustments to dosing intervals were made based on monitoring of trough levels at Weeks 4, 16, 26, and 39

Average dosing interval for fixed-dose (100 IU/kg) arm during last 3 months on study[3]



- Overall median dosing interval on study was 12.5 days (interquartile range [IQR]: 10.4-13.4)

Safety of ALPROLIX in clinical trials[1]

- Zero inhibitors, vascular thrombotic events, and anaphylaxis were reported
- The most commonly reported adverse reactions among adults and adolescents were headache, oral paresthesia, and obstructive uropathy

Please see additional Important Safety Information on last page and Full Prescribing Information.

For perioperative use[1]

For minor surgery: a single infusion to reach factor IX level of 50 to 80 IU/dL may be sufficient

- Repeat as needed after 24 to 48 hours until bleeding stops and healing is achieved

For major surgery: initial infusion to reach factor IX level of 60 to 100 IU/dL

- Consider a repeat dose after 6 to 10 hours and then every 24 hours for the first 3 days, then every 48 hours until bleeding stops and healing is achieved
- Consider determining the patient's in vivo recovery (in IU/dL per IU/kg) prior to elective major surgery; verify that the target factor IX level has been achieved prior to major surgery and for major bleeds

On-demand treatment and control of bleeding episodes[1]

For minor and moderate bleeds: initial dose to reach a target circulating factor IX level of 30 to 60 IU/dL

- Repeat every 48 hours as needed if there is further evidence of bleeding

For major bleeds: initial dose to reach a target circulating factor IX level of 80 to 100 IU/dL

- Consider a repeat dose after 6 to 10 hours and then every 24 hours for 3 days, then every 48 hours until healing is achieved

Estimate the required dose or the expected in vivo peak increase in factor IX level using the following formulas:

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)

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ALPROLIX® is packaged with your patients in mind[1]

ALPROLIX has 6 vial options, including a 4000-IU vial

Graphic is for illustrative purposes only.

- ALPROLIX is supplied in single-use vials nominally containing 250, 500, 1000, 2000, 3000, or 4000 IU per vial. The actual factor IX potency is stated on each ALPROLIX vial
- Liquid diluent comes in a prefilled syringe

ALPROLIX comes in a small, stackable case that includes:

- Single-use glass vial of ALPROLIX
- Prefilled syringe containing 5 mL diluent and sealed with a plunger stopper and tip cap
- Sterile vial adapter (reconstitution device)

Important Safety Information

- Formation of neutralizing antibodies (inhibitors) to Factor IX has been reported following administration of ALPROLIX, including in previously untreated patients. Patients using ALPROLIX should be monitored for the development of Factor IX inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor IX levels have been achieved and maintained.

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WARNINGS AND PRECAUTIONS:

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The use of Factor IX products has been associated with the development of thromboembolic complications.

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

ADVERSE REACTIONS:

Common adverse reactions (incidence ≥1%) observed in clinical trials were headache, oral paresthesia, and obstructive uropathy.

Please see Full Prescribing Information.

References: 1. ALPROLIX® [package insert]. Waltham, MA: Bioverativ®, a Sanofi Company; 2018. **2.** Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *N Engl J Med*. 2013;369(24):2313-2323. **3.** Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *N Engl J Med.* 2013;369(suppl):1-14. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1305074/suppl_file/nejmoa1305074_appendix.pdf. Accessed May 2, 2018.

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