Eftrenonacog alfa

IDENTIFICATION

Name	Eftrenonacog alfa
Accession Number	DB11608
Type	Biotech
Groups	Approved, Investigational
Biologic Classification	Protein Based Therapies Blood factors
Description	Eftrenonacog alfa is a long-acting recombinant fusion protein used in the treatment of hemophilia B. It is comprised of a single molecule of human factor IX (FIX) covalently linked to the constant region (Fc) domain of human IgG1 via recombinant DNA technology in a human embryonic kidney cell line (HEK293H) [1]. The presence of the Fc domain extends the terminal half-life which confers clinical benefits of prolonged therapeutic efficacy, less frequent intravenous injections for patient convenience and improved adherence to prophylaxis. Hemophilia B is a blood disorder with an incidence of approximately once every 30,000 male births in all populations and ethnic groups [2]. It is an X-linked genetic disease caused by mutation of the gene for coagulation protein factor IX (FIX), leading to decreased levels of endogenous factor IX and increased susceptibility to recurrent bleeding episodes caused spontaneously or as a result of accidental or surgical trauma [Label]. When untreated, most patients die from bleeding complications before 25 years of age [2]. Eftrenonacog alfa acts as a replacement therapy to restore the levels of factor IX and allow normal hemostasis. Eftrenonacog alfa was developed and marketed as Alprolix for intravenous injection by Biogen. It was first approved by the FDA in March 2014 and later approved by the EMA in May 2016. Eftrenonacog alfa treatment demonstrated good tolerability with no reports of inhibitor development in clinical studies [1].
Protein chemical formula	Not Available
Protein average weight	98000.0 Da (Approximate)
Sequences	Not Available
Synonyms	Coagulation factor IX recombinant immunoglubulin g1 fusion protein Recombinant human coagulation factor IX, FC Fusion protein

Prescription Products

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NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END	
Alprolix	Kit	1000 [iU]/5mL	Intravenous	Biogen	2014-05-05	Not applicable	
Alprolix	Kit; Powder, for solution	250 unit	Intravenous	Bioverativ Canada Inc	Not applicable	Not applicable	

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END	
Alprolix	Kit	4000 [iU]/5mL	Intravenous	Bioverativ Therapeutics Inc.	2016-10-28	Not applicable	
Alprolix	Kit	500 [iU]/5mL	Intravenous	Biogen	2014-05-05	Not applicable	
Alprolix	Kit; Powder, for solution	3000 unit	Intravenous	Bioverativ Canada Inc	2016-01-15	Not applicable	
Alprolix	Kit	1000 [iU]/5mL	Intravenous	Bioverativ Therapeutics Inc.	2014-05-05	Not applicable	
Alprolix	Kit	3000 [iU]/5mL	Intravenous	Biogen	2014-05-05	Not applicable	
Alprolix	Kit; Powder, for solution	4000 unit	Intravenous	Bioverativ Canada Inc	Not applicable	Not applicable	

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Categories Hemostatics

UNII 02E00T2QDE

CAS number 1270012-74-2

PHARMACOLOGY

Indication Indicated for the treatment and prophylaxis of bleeding in patients of all age with haemophilia B (congenital factor IX deficiency).

Associated Conditions Bleeding

Postoperative Hemorrhages

Pharmacodynamics In two multinational, phase III studies in previously treated children, adolescents and adults with severe haemophilia B, eftrenonacog alfa prophylaxis resulted in low median annualized bleeding rates (ABRs), and was associated with reductions in median weekly factor consumption and dosing frequency compared with pre-study FIX regimens. The extension of those studies demonstrated effectiveness in the treatment of bleeding episodes and when used in the perioperative setting in all age groups [1]. In animal models, a single intravenous dose of eftrenonacog alfa displayed half values approximately three- to four-fold longer than those seen with recombinant FIX [1].

Mechanism of action The coagulation protein factor IX (FIX) is a vitamin K-dependent coagulation factor and one of the critical serine proteases involved in the coagulation cascade. Upon activation by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway, factor IX, in combination with factor VIII, activates factor X. Activated factor X mediates the conversion of prothrombin to thrombin which sequentially leads to thrombin converting fibrinogen into fibrin. A blood clot is then formed [Label]. With a mutation in the gene encoding the coagulation protein factor IX (FIX), patients with hemophilia B have factor IX deficiency and are at high risk for recurrent bleeding episodes.

Eftrenonacog alfa is composed of a single molecule of recombinant FIX (rFIX) covalently fused to the dimeric Fc domain of immunoglobulin (Ig) G1 (rFIXFc). It serves as a replacement therapy to increase the plasma levels of factor IX thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies [Label]. The Fc region of human immunoglobulin G1 binds with the neonatal Fc receptor which 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. The binding

of eftrenonacog alfa to the neonatal Fc receptor delays degradation and recycles the fusion protein back into circulation for increased plasma half life and prolonged therapeutic action [Label].

Absorption	Following administration of a single intravenous dose of 50 IU/kg of eftrenonacog alfa in patients ≥19 years of age with hemophilia B, the mean peak plasma concentration (Cmax) was 46.10 IU/dL [Label]. The mean area under the FIX activity time curve (AUC) was 31.58 Uxh/dL per IU/kg [Label]. In pediatric and adolescent patients (< 18 years of age) receiving the same dose, the mean AUC ranged from 22.71 to 29.50 Uxh/dL per IU/kg [Label].
Volume of distribution	Following administration of a single intravenous dose of 50 IU/kg of eftrenonacog alfa in patients ≥19 years of age with hemophilia B, the mean volume of distribution at steady-state (Vss) was 303.4 mL/kg [Label]. In pediatric and adolescent patients (< 18 years of age) receiving the same dose, the mean Vss ranged from 289 to 365.1 mL/kg [Label].
Protein binding	Not Available
Metabolism	The Fc domain of eftrenonacog alfa is expected to undergo lysosomal degradation while the remaining recombinant FIX (rFIX) portion is expected to be metabolized by the same pathway as endogenous factor IX.
Route of elimination	Eftrenonacog alfa is expected to undergo renal clearance [2].
Half life	Following administration of a single intravenous dose of 50 IU/kg of eftrenonacog alfa in patients ≥19 years of age with hemophilia B, the mean terminal half life (t1/2) was 77.6 hours [Label]. In pediatric and adolescent patients (< 18 years of age) receiving the same dose, the mean t1/2 ranged from 66.49 to 82.22 hours [Label].
Clearance	Following administration of a single intravenous dose of 50 IU/kg of eftrenonacog alfa in patients ≥19 years of age with hemophilia B, the mean clearance (CL) was 3.17 mL/h/kg [Label]. In pediatric and adolescent patients (< 18 years of age) receiving the same dose, mean CL ranged from 3.390 to 4.365 mL/h/kg [Label].
Toxicity	Based on findings from a rabbit thrombogenicity test and rat or monkey repeated-dose toxicity studies, eftrenonacog alfa displays no special hazards for humans. Studies to investigate the genotoxicity, carcinogenicity, toxicity to reproduction or embryo-foetal development have not been conducted. Eftrenonacog alfa has shown to cross the placenta in small amounts according to a mouse placental transfer study [Label].
Affected organisms	Not Available
Pathways	Not Available
Pharmacogenomic Effects/ADRs	Not Available

INTERACTIONS

Drug Interactions	Not Available
Food Interactions	Not Available

REFERENCES

General References

1. Hoy SM: Eftrenonacog Alfa: A Review in Haemophilia B. Drugs. 2017 Jul;77(11):1235-1246. doi: 10.1007/s40265-017-0778-1. [PubMed:28646426]

2. Miguelino MG, Powell JS: Clinical utility and patient perspectives on the use of extended half-life rFIXFc in the management of hemophilia B. Patient Prefer Adherence. 2014 Aug 8;8:1073-83. doi: 10.2147/PPA.S54951. eCollection 2014. [PubMed:25143713]

External Links	PubChem Substance	347911218
AHFS Codes	20:28.16 — Hemostatics	
FDA label	Download (448 KB)	

CLINICAL TRIALS

Clinical Trials

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PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
0	Recruiting	Treatment	Hemophilia / Menstrual Flow Excessive	1
1	Completed	Treatment	Congenital Hematological Disorder / Haemophilia B	1
1	Completed	Treatment	Hereditary factor IX deficiency	1
3	Active Not Recruiting	Treatment	Hereditary factor IX deficiency	1
3	Completed	Treatment	Hereditary factor IX deficiency	1
3	Completed	Treatment	Severe Hemophilia B	1
Not Available	Not Yet Recruiting	Not Available	Hereditary factor IX deficiency	1
Not Available	Recruiting	Not Available	Haemophilia B	1
Not Available	Recruiting	Not Available	Haemophilia B / Hemophilia A	1
Not Available	Recruiting	Not Available	Hemophilia	1

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PHARMACOECONOMICS

Manufacturers	Not Available
Packagers	Not Available

Dosage forms

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FORM	ROUTE	STRENGTH
Kit	Intravenous	1000 [iU]/5mL
Kit	Intravenous	2000 [iU]/5mL
Kit	Intravenous	250 [iU]/5mL
Kit	Intravenous	3000 [iU]/5mL
Kit	Intravenous	4000 [iU]/5mL
Kit	Intravenous	500 [iU]/5mL
Kit; powder, for solution	Intravenous	1000 unit
Kit; powder, for solution	Intravenous	2000 unit
Kit; powder, for solution	Intravenous	250 unit
Kit; powder, for solution	Intravenous	3000 unit

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Prices	Not Available
Patents	Not Available

PROPERTIES

Experimental Properties	Not Available

TAXONOMY

Description	Not Available
Kingdom	Organic Compounds
Super Class	Organic Acids
Class	Carboxylic Acids and Derivatives
Sub Class	Amino Acids, Peptides, and Analogues
Direct Parent	Peptides
Alternative Parents	Not Available
Substituents	Not Available
Molecular Framework	Not Available
External Descriptors	Not Available

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