Albutrepenonacog alfa

Targets (1) Enzymes (1) Biointeractions (2)

IDENTIFICATION

Name

Albutrepenonacog alfa

Accession Number

DB13884

Type

Biotech

Groups

Approved

Biologic Classification

Protein Based Therapies
Blood factors / Fusion proteins

Description

Albutrepenonacog alfa (rIX-RFP) is a recombinant fusion protein that links a recombinant coagulation factor IX (rFIX) with a recombinant human albumin (rAlbumin).[1] It was developed by CSL Behring Canada, Inc and approved by Health Canada on April 26, 2017. It was also approved by FDA and EMA in 2016. It is currently marketed in the forms of 250, 500, 1000 and 2000 IU/vial.[5]

Protein structure

Protein chemical formula

$C_{5077}N_{7846}O_{1588}PS_{67}$

Protein average weight

125000.0 Da

Sequences

```
>>Albutrepenonacog alfa<<<<
YNSGKLEEFVQGNLERECMEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGG
SCKDDINSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAEN
QKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTR
VVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEE
TEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLRSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTPVSQT
SKLTRAETVFPDVDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVT
EFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKD
DNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTE
CCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE
FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKS
HCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLL
RLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNAL
LVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT
PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQT
ALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL
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Synonyms

Coagulation factor IX (recombinant), albumin fusion protein

Prescription Products

Search

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END			

Idelvion	Injection, powder, for solution	240 IU	Intravenous	Csl Behring	2016-05-11	Not applicable	
Idelvion	Kit	2000 [iU]/5mL		Csl Behring Recombinant Facility Ag	2016-03-04	Not applicable	
Idelvion	Kit	250 [iU]/2.5mL		Csl Behring Recombinant Facility Ag	2016-03-04	Not applicable	
Idelvion	Injection, powder, for solution	1000 IU	Intravenous	Csl Behring	2016-05-11	Not applicable	
Idelvion	Kit	1000 [iU]/2.5mL		Csl Behring Recombinant Facility Ag	2016-03-04	Not applicable	
Idelvion	Kit; Powder, for solution	250 unit	Intravenous	Csl Behring	Not applicable	Not applicable	
Idelvion	Injection, powder, for solution	500 IU	Intravenous	Csl Behring	2016-05-11	Not applicable	
Idelvion	Kit	3500 [iU]/5mL		Csl Behring Recombinant Facility Ag	2018-05-30	Not applicable	
Idelvion	Kit	500 [iU]/2.5mL		Csl Behring Recombinant Facility Ag	2016-03-04	Not applicable	

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Categories

Hemostatics

UNII

A57KX1VL5P

CAS number

1257448-54-4

Indication

Under the EMA and FDA, rIX-RFP is indicated in the treatment of hemophilia B.[6] For Health Canada, rIX-FRP is also indicated to prevent or reduce bleeding episodes.[5]

Hemophilia B is the second most common type of hemophilia. It is a rare inherited bleeding disorder caused by reduced or absent levels of factor IX (FIX). The FIX is a vitamin K-dependent plasma protease that when activated is involved in the blood coagulation cascade.[2] The hemophilia B is caused by mutations in the *FIX* gene which can cause different phenotypes. The severe form is characterized by the presence of spontaneous and recurring bleeds into the joints and muscles and excessive bleeding after trauma or surgery.[3]

Associated Conditions

Postoperative Hemorrhages

Bleeding episodes

Pharmacodynamics

Clinical trials with rIX-RFP in patients with moderately to severe hemophilia B demonstrated a lower annualized spontaneous, total and joint bleeding rates. It was also efficient against bleeding episodes and maintenance of hemostasis in the perioperative setting when compared with on-demand treatment. The administration of rIX-RFP presented no reports of inhibitor development.[1]

Mechanism of action

The current therapies against hemophilia B are hampered by the short half-life of the replacement FIX therapy.[1] Thus, to solve this problem, in rIX-RFP there is the fusion of rFIX with rAlbumin which presents a much longer half-life and it does not present interactions with the immune system.[1]

The administration of rIX-RFP increases the plasma concentration of FIX, thus addressing the coagulation deficiency of the patient. rIX-RFP is able to circulate in the plasma as an intact zymogen thanks to the pH-dependent binding to FcRn which is a normal protection pathway from lysosomal degradation of albumin. When the FIX is needed, rAlbumin is cleaved by the same proteases that activate the FIX.[1]

Absorption

rIX-RFP absorption is very rapid as it is directly administered intravenously. In clinical trials, the maximum plasma concentration, area under the curve and mean residence time are reported to be approximately 55 IU/dL, 5500 IU.h/dL and 125 hours respectively.[1]

Volume of distribution

The reported volume of distribution for rIX-RFP according to phase I/II and III clinical trials is 95 ml/kg.[4]

Protein binding

This pharmacokinetic value is not relevant as this drug is part of the plasma proteins.

Metabolism

The metabolism of rIX-RFP is not relevant as it is a recombinant protein and it is thought to be metabolized to peptides and amino acids.[7]

Route of elimination

rIX-RFP is mainly eliminated in the urine. In preclinical studies, the distribution of urine and feces 240 hours post administration corresponded to 72.9% and 4.3% of the administered dose respectively. The elimination on the first 24 hours in urine and feces only corresponded to the 39.9% and 0.92% of the dose.[7]

Half life

The fusion of the rFIX with rAlbumin prolongs the elimination half-life of rIX-RFP in the circulation. The reported half-life in clinical trials is 92 hours.[1]

Clearance

In clinical trials, the weight-adjusted clearance in children and adults is reported to be 1.1 and 0.9 ml/h/kg.[1]

Toxicity

rIX-RFP is very well tolerated.[1]Mutaginicity trials were performed and they confirmed an absent mutagenic potential.[5]Fertility studies have not been performed. Developmental studies are not of major importance as there is a very low rate of incidence of hemophilia B in females.

Pathways

Not Available

Pharmacogenomic Effects/ADRs

Not Available

INTERACTIONS

Drug Interactions

ALL DRUGS | APPROVED | VET APPROVED | NUTRACEUTICAL | ILLICIT | WITHDRAWN | INVESTIGATIONAL | EXPERIMENTAL

Search

DRUG	INTERACTION
Acetaminophen	Acetaminophen may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Acetylsalicylic acid	Acetylsalicylic acid may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Acyclovir	Acyclovir may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Adefovir Dipivoxil	Adefovir Dipivoxil may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Almotriptan	Almotriptan may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Alprazolam	Alprazolam may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Amantadine	Amantadine may decrease the excretion rate of Albutrepenonacog alfa which could result in a higher serum level.
Amiloride	Amiloride may increase the excretion rate of Albutrepenonacog alfa which could result in a lower serum level and potentially a reduction in efficacy.

	in a higher serum level.

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Food Interactions

Not Available

REFERENCES

General References

1. Lyseng-Williamson KA: Coagulation Factor IX (Recombinant), Albumin Fusion Protein (Albutrepenonacog Alfa; Idelvion((R))): A Review of Its Use in Haemophilia B. Drugs. 2017 Jan;77(1):97-106. doi: 10.1007/s40265-016-0679-8. [PubMed:27988873]
2. Nazeef M, Sheehan JP: New developments in the management of moderate-to-severe hemophilia B. J Blood Med. 2016 Apr 1;7:27-38. doi: 10.2147/JBM.S81520. eCollection 2016. [PubMed:27099538]
3. Goodeve AC: Hemophilia B: molecular pathogenesis and mutation analysis. J Thromb Haemost. 2015 Jul;13(7):1184-95. doi: 10.1111/jth.12958. Epub 2015 May 18. [PubMed:25851415]
4. Morfini M: Pharmacokinetic drug evaluation of albutrepenonacog alfa (CSL654) for the treatment of hemophilia. Expert Opin Drug Metab Toxicol. 2016 Oct 2:1-7. doi: 10.1080/17425255.2016.1240168. [PubMed:27677190]
5. Health Canada monograph [Link]
6. EMA Product report [Link]
7. PMDA report on the deliberation [Link]

External Links

PubChem Substance

347911453

AHFS Codes

20:28.16 — Hemostatics

FDA label

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CLINICAL TRIALS

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
Not Available	Recruiting	Not Available	Hemophilia	1

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PHARMACOECONOMICS

Manufacturers

Not Available

Packagers

Not Available

Dosage forms

Search

FORM	ROUTE	STRENGTH
Injection, powder, for solution	Intravenous	1000 IU
Injection, powder, for solution	Intravenous	2000 IU
Injection, powder, for solution	Intravenous	240 IU
Injection, powder, for solution	Intravenous	500 IU
Kit		1000 [iU]/2.5mL
Kit		2000 [iU]/5mL
Kit		250 [iU]/2.5mL
Kit		3500 [iU]/5mL
Kit		500 [iU]/2.5mL
Kit; powder, for solution	Intravenous	250 unit

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Prices

Not Available

PROPERTIES

State

Solid

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

External Descriptors

Not Available

TARGETS

1. Coagulation factor X

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Activator

General Function

Serine-type endopeptidase activity

Specific Function

Factor Xa is a vitamin K-dependent glycoprotein that converts prothrombin to thrombin in the presence of factor Va, calcium and phospholipid during blood clotting.

Gene Name

F10

Uniprot ID

P00742

Uniprot Name

Coagulation factor X

Molecular Weight

(Albutrepenonacog Alfa; Idelvion((R))): A Review of Its Use in Haemophilia B. Drugs. 2017 Jan;77(1):97-106. doi: 10.1007/s40265-016-0679-8. [PubMed:27988873]

ENZYMES

1. Coagulation factor VIII

Kind

Protein

Organism

Human

Pharmacological action

No

Actions

Substrate

General Function

Oxidoreductase activity

Specific Function

Factor VIII, along with calcium and phospholipid, acts as a cofactor for factor IXa when it converts factor X to the activated form, factor Xa.

Gene Name

F8

Uniprot ID

P00451

Uniprot Name

Coagulation factor VIII

1. Lyseng-Williamson KA: Coagulation Factor IX (Recombinant), Albumin Fusion Protein (Albutrepenonacog Alfa; Idelvion((R))): A Review of Its Use in Haemophilia B. Drugs. 2017 Jan;77(1):97-106. doi: 10.1007/s40265-016-0679-8. [PubMed:27988873]

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