



Drotrecogin alfa

Targets (12)

IDENTIFICATION

Name

Drotrecogin alfa

Accession Number

DB00055 (BTD00068, BIOD00068)

Type

Biotech

Groups

Approved, Investigational, Withdrawn

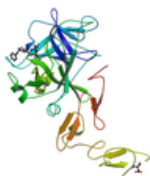
Biologic Classification

Protein Based Therapies
Other protein based therapies

Description

Drotrecogin alfa is activated human protein C that is synthesized by recombinant DNA technology. It is a glycoprotein of approximately 55 kilodalton molecular weight, consisting of a heavy chain and a light chain linked by a disulfide bond. Drotrecogin alfa was withdrawn from the market after a major study indicated that it was not effective in improving outcomes in patients with sepsis.

Protein structure



Protein chemical formula

$C_{1786}H_{2779}N_{509}O_{519}S_{29}$

Protein average weight

55000.0 Da

Sequences

>Heavy chain
LIDGKMTRRGDSPWQVLLDSK KKLACGAVLIHPSWVLTAAHCMDESKLLVRLGEYDLR

CDKQPCACLDGSDGFFIVASTHTDITWLEVEVSWLGGCELEHNTGVYIKVSKTEPWHTGHTND
KEAPQKSWAP

>Light chain
SKHVDGDQCLVLPLEHPCASLCCGHGTCIXGIGSFSCDCRSWEGRFQREVSFLNCSLD
NGGCTHYCLEEVGWRRCSAPGYKLGDDLQCHPAVKFPCGRPWKRMEKKRSHL

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Synonyms

Activated protein C
Blood coagulation factor XIV (human)
Drotrecogin alfa (activated)
Drotrecogin alfa (activated), lyophilized
Drotrecogin alfa activated
Drotrecogin alfa, activated
Drotrecogin-alfa
Recombinant human activated protein C (rH-APC)

External IDs [i](#)

LY203638

Prescription Products

Search



NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END			
Xigris (20mg/vial)	Powder, for solution	20 mg	Intravenous	Eli Lilly & Co. Ltd.	2003-03-25	2011-11-14			
Xigris (5mg/vial)	Powder, for solution	5 mg	Intravenous	Eli Lilly & Co. Ltd.	2003-02-20	2011-11-14			

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Unapproved/Other Products [i](#)

Search

NAME	INGREDIENTS	DOSAGE	ROUTE	LABELLER	MARKETING START	MARKETING END			
Xigris	Drotrecogin alfa (5 mg)	Injection, powder, for solution	Intravenous	Eli Lilly Nederland B.V.	2002-08-22	2011-10-25			
Xigris	Drotrecogin alfa (20 mg)	Injection, powder, for solution	Intravenous	Eli Lilly Nederland B.V.	2002-08-22	2011-10-25			

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International/Other Brands

**Categories**[Amino Acids, Peptides, and Proteins](#)[Anti-Infective Agents](#)[Biological Factors](#)[Blood and Blood Forming Organs](#)[Blood Coagulation Factor Inhibitors](#)[Blood Proteins](#)[Carbohydrates](#)[Enzyme Precursors](#)[Enzymes](#)[Enzymes and Coenzymes](#)[Fibrinolytic Agents](#)[Glycoconjugates](#)[Glycoproteins](#)[Proteins](#)[Recombinant Activated Protein C](#)**UNII**[JGH8MYC891](#)**CAS number**

98530-76-8

PHARMACOLOGY**Indication**

For reduction of mortality in patients with severe sepsis.

Structured Indications ⓘ

Not Available

Pharmacodynamics

Drotrecogin alfa is activated human protein C that is synthesized by recombinant DNA technology. It is a glycoprotein of approximately 55 kilodalton molecular weight, consisting of a heavy chain and a light chain linked by a disulfide bond. Drotrecogin alfa inhibits factor Va and VIIIa, thereby reducing the coagulability of blood.

Mechanism of action

Activated protein C combines with protein S on platelet surfaces and then degrades factor Va and factor VIIIa, thereby reducing blood coagulability.

[A Coagulation factor VIII](#) ⓘ



[Coagulation factor V](#)

multitarget

Human

[Plasminogen activator inhibitor 1](#)

Not Available

Human

[Thrombomodulin](#)

Not Available

Human

[Vitamin K-dependent protein S](#)

Not Available

Human

[Ceruloplasmin](#)

Not Available

Human

[Prothrombin](#)

Not Available

Human

[Platelet factor 4](#)

Not Available

Human

[Plasma serine protease inhibitor](#)

Not Available

Human

[Serpins B6](#)

Not Available

Human

[Vitamin K-dependent gamma-carboxylase](#)

Not Available

Human

[Endothelial protein C receptor](#)

Not Available

Human

Absorption

Not Available

Volume of distribution

Not Available

**Metabolism**

Not Available

Route of elimination

Not Available

Half life

5.5 hours (mammalian reticulocytes, in vitro).

Clearance

- 40 L/hr [severe sepsis adults]
- 30 +/- 8 L/hr [patients without sepsis undergoing hemodialysis]
- 28 +/- 9 L/hr [heathy]

Toxicity

Not Available

Affected organisms

Humans and other mammals

Pathways

Not Available

Pharmacogenomic Effects/ADRs ⓘ

Not Available

INTERACTIONS

Drug Interactions ⓘ

Search

DRUG	↕ INTERACTION	↕ DRUG GROUP
Abciximab	Drotrecogin alfa may increase the anticoagulant activities of Abciximab.	Approved
Acenocoumarol	Drotrecogin alfa may increase the anticoagulant activities of Acenocoumarol.	Approved, Investigational
Acetylsalicylic acid	The risk or severity of adverse effects can be increased when Acetylsalicylic acid is combined with Drotrecogin alfa.	Approved, Vet Approved
Aloxiprin	The risk or severity of adverse effects can be increased when Aloxiprin is combined with Drotrecogin alfa.	Experimental
Alprostadil	Alprostadil may increase the anticoagulant activities of Drotrecogin alfa.	Approved, Investigational
Aminosaliclyic Acid	The risk or severity of adverse effects can be increased when Aminosaliclyic Acid is combined with Drotrecogin alfa.	Approved
Anagrelide	Anagrelide may increase the anticoagulant activities of Drotrecogin alfa.	Approved
Ancrod	Drotrecogin alfa may increase the anticoagulant activities of Ancrod.	Approved, Investigational
Andrographolide	Andrographolide may increase the anticoagulant activities of Drotrecogin alfa.	Investigational



Antithrombin III human	Drotrecogin alfa may increase the anticoagulant activities of Antithrombin III human.	Approved
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Food Interactions

Not Available

REFERENCES

General References

Not Available

External Links

UniProt

[P04070](#)

Genbank

[M11228](#)

PubChem Substance

[46505655](#)

Therapeutic Targets Database

[DAP000151](#)

PharmGKB

[PA131548935](#)

RxList

[RxList Drug Page](#)

Drugs.com

[Drugs.com Drug Page](#)

Wikipedia

[Drotrecogin_alfa](#)

ATC Codes

[B01AD10 — Drotrecogin alfa \(activated\)](#)

- [B01AD — Enzymes](#)
- [B01A — ANTITHROMBOTIC AGENTS](#)
- [B01 — ANTITHROMBOTIC AGENTS](#)
- [B — BLOOD AND BLOOD FORMING ORGANS](#)

FDA label

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CLINICAL TRIALS



Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
0	Completed	Treatment	Lung Inflammation	1
2	Completed	Treatment	End Stage Renal Disease (ESRD)	1
2	Completed	Treatment	Sepsis / Shock, Septic	1
2	Completed	Treatment	Severe Sepsis	1
2	Completed	Treatment	Submassive Pulmonary Embolism	1
2	Terminated	Treatment	Respiratory Distress Syndrome, Adult	1
2	Terminated	Treatment	Strokes	1
3	Completed	Treatment	Arterial Hypotension / Sepsis	1
3	Completed	Treatment	Sepsis	3
4	Completed	Treatment	Acute Pancreatitis (AP)	1
4	Completed	Treatment	Hematopoietic Stem Cell Transplantation (HSCT) / Infection NOS / Neoplasms, Hematologic / Sepsis	1
4	Completed	Treatment	Sepsis	2
4	Completed	Treatment	Sepsis / Shock, Septic	1
4	Completed	Treatment	Severe Sepsis	1
4	Completed	Treatment	Shock, Septic	1
Not Available	Completed	Not Available	Sepsis	1

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PHARMACOECONOMICS

Manufacturers

Not Available

Packagers[DSM Corp.](#)[Eli Lilly & Co.](#)**Dosage forms**

Search

FORM	ROUTE	STRENGTH
Injection, powder, for solution	Intravenous	20 mg
Injection, powder, for solution	Intravenous	5 mg
Powder, for solution	Intravenous	20 mg
Powder, for solution	Intravenous	5 mg

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UNIT DESCRIPTION	↕ COST	↕ UNIT	↕
Xigris 20 mg vial	1481.66USD	vial	
Xigris 5 mg vial	370.42USD	vial	

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Patents

PATENT NUMBER	↕ PEDIATRIC EXTENSION	↕ APPROVED	↕ EXPIRES (ESTIMATED)	↕	↕
CA2139468	No	2007-08-21	2015-01-03		
CA2036894	No	2002-01-15	2011-02-22		

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PROPERTIES**State**

Liquid

Experimental Properties

PROPERTY	VALUE	SOURCE
hydrophobicity	-0.291	Not Available
isoelectric point	6.78	Not Available

TAXONOMY**Description**

Not Available

Kingdom

Organic Compounds

Super Class

Organic Acids

Class

Carboxylic Acids and Derivatives

Sub Class

**Direct Parent**

Peptides

Alternative Parents

Not Available

Substituents

Not Available

Molecular Framework

Not Available

External Descriptors

Not Available

TARGETS

1. Coagulation factor VIII**Kind**

Protein

Organism

Human

Pharmacological action Yes**Actions** Multitarget**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

Molecular Weight

267007.42 Da

References



Haemost. 1997 May;11(5):926-33. [[PubMed:9184404](#)]

2. Colin G, Annane D: Corticosteroids and human recombinant activated protein C for septic shock. Clin Chest Med. 2008 Dec;29(4):705-12, x. doi: 10.1016/j.ccm.2008.06.009. [[PubMed:18954704](#)]
3. Chen X, Ji ZL, Chen YZ: TTD: Therapeutic Target Database. Nucleic Acids Res. 2002 Jan 1;30(1):412-5. [[PubMed:11752352](#)]

2. Coagulation factor V

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Multitarget

General Function

Copper ion binding

Specific Function

Central regulator of hemostasis. It serves as a critical cofactor for the prothrombinase activity of factor Xa that results in the activation of prothrombin to thrombin.

Gene Name

F5

Uniprot ID

[P12259](#)

Uniprot Name

Coagulation factor V

Molecular Weight

251701.245 Da

References

1. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001 Mar 8;344(10):699-709. [[PubMed:11236773](#)]
2. Kanji S, Devlin JW, Piekos KA, Racine E: Recombinant human activated protein C, drotrecogin alfa (activated): a novel therapy for severe sepsis. Pharmacotherapy. 2001 Nov;21(11):1389-402. [[PubMed:11714212](#)]
3. Lyseng-Williamson KA, Perry CM: Drotrecogin alfa (activated). Drugs. 2002;62(4):617-30; discussion 631-2. [[PubMed:11893230](#)]
4. Joyce DE, Grinnell BW: Recombinant human activated protein C attenuates the inflammatory response in endothelium and monocytes by modulating nuclear factor-kappaB. Crit Care Med. 2002 May;30(5 Suppl):S288-93. [[PubMed:12004250](#)]
5. Poe K: Drotrecogin alfa (activated) approved for treatment of severe sepsis. J Am Pharm Assoc (Wash). 2002 May-Jun;42(3):520-2. [[PubMed:12030642](#)]
6. Chen X, Ji ZL, Chen YZ: TTD: Therapeutic Target Database. Nucleic Acids Res. 2002 Jan 1;30(1):412-5. [[PubMed:11752352](#)]

**Kind**

Protein

Organism

Human

Pharmacological action

Unknown

General Function

Serine-type endopeptidase inhibitor activity

Specific Function

Serine protease inhibitor. This inhibitor acts as 'bait' for tissue plasminogen activator, urokinase, protein C and matriptase-3/TMPRSS7. Its rapid interaction with PLAT may function as a major con...

Gene Name

SERPINE1

Uniprot ID[P05121](#)**Uniprot Name**

Plasminogen activator inhibitor 1

Molecular Weight

45059.695 Da

References

1. Carr ME: Diabetes mellitus: a hypercoagulable state. J Diabetes Complications. 2001 Jan-Feb;15(1):44-54. [[PubMed:11259926](#)]
2. Cerchiara E, Tirindelli MC, Giannetti B, Dicuonzo G, Avvisati G: [The numerous properties of the anticoagulant protein C]. Clin Ter. 2007 Mar-Apr;158(2):181-7. [[PubMed:17566522](#)]
3. Idell S: Endothelium and disordered fibrin turnover in the injured lung: newly recognized pathways. Crit Care Med. 2002 May;30(5 Suppl):S274-80. [[PubMed:12004248](#)]
4. Dhainaut JF, Yan SB, Margolis BD, Lorente JA, Russell JA, Freebairn RC, Spapen HD, Riess H, Basson B, Johnson G 3rd, Kinasewitz GT: Drotrecogin alfa (activated) (recombinant human activated protein C) reduces host coagulopathy response in patients with severe sepsis. Thromb Haemost. 2003 Oct;90(4):642-53. [[PubMed:14515185](#)]

4. Thrombomodulin**Kind**

Protein

Organism

Human

Pharmacological action

Unknown

General Function

Transmembrane signaling receptor activity

Specific Function

**Gene Name**

THBD

Uniprot ID[P07204](#)**Uniprot Name**

Thrombomodulin

Molecular Weight

60328.72 Da

References

1. Gresele P, Agnelli G: Novel approaches to the treatment of thrombosis. Trends Pharmacol Sci. 2002 Jan;23(1):25-32. [[PubMed:11804648](#)]
2. Pineda AO, Chen ZW, Caccia S, Cantwell AM, Savvides SN, Waksman G, Mathews FS, Di Cera E: The anticoagulant thrombin mutant W215A/E217A has a collapsed primary specificity pocket. J Biol Chem. 2004 Sep 17;279(38):39824-8. Epub 2004 Jul 13. [[PubMed:15252033](#)]
3. McCachren SS, Diggs J, Weinberg JB, Dittman WA: Thrombomodulin expression by human blood monocytes and by human synovial tissue lining macrophages. Blood. 1991 Dec 15;78(12):3128-32. [[PubMed:1660324](#)]
4. Shirai T, Shiojiri S, Ito H, Yamamoto S, Kusumoto H, Deyashiki Y, Maruyama I, Suzuki K: Gene structure of human thrombomodulin, a cofactor for thrombin-catalyzed activation of protein C. J Biochem. 1988 Feb;103(2):281-5. [[PubMed:2836377](#)]
5. Boffa MC, Burke B, Haudenschild C: [Different localization of thrombomodulin]. Ann Biol Clin (Paris). 1987;45(2):191-7. [[PubMed:3039877](#)]

5. Vitamin K-dependent protein S**Kind**

Protein

Organism

Human

Pharmacological actionUnknown**General Function**

Endopeptidase inhibitor activity

Specific Function

Anticoagulant plasma protein; it is a cofactor to activated protein C in the degradation of coagulation factors Va and VIIIa. It helps to prevent coagulation and stimulating fibrinolysis.

Gene Name

PROS1

Uniprot ID[P07225](#)**Uniprot Name**

Vitamin K-dependent protein S



References

1. Cvirn G, Gallistl S, Koestenberger M, Kutschera J, Leschnik B, Muntean W: Alpha 2-macroglobulin enhances prothrombin activation and thrombin potential by inhibiting the anticoagulant protein C/protein S system in cord and adult plasma. *Thromb Res.* 2002 Mar 1;105(5):433-9. [[PubMed:12062545](#)]
2. Hesselvik JF, Malm J, Dahlback B, Blomback M: Protein C, protein S and C4b-binding protein in severe infection and septic shock. *Thromb Haemost.* 1991 Feb 12;65(2):126-9. [[PubMed:1828915](#)]
3. Cosio FG, Harker C, Batard MA, Brandt JT, Griffin JH: Plasma concentrations of the natural anticoagulants protein C and protein S in patients with proteinuria. *J Lab Clin Med.* 1985 Aug;106(2):218-22. [[PubMed:3160800](#)]

6. Ceruloplasmin

Kind

Protein

Organism

Human

Pharmacological action

Unknown

General Function

Ferroxidase activity

Specific Function

Ceruloplasmin is a blue, copper-binding (6-7 atoms per molecule) glycoprotein. It has ferroxidase activity oxidizing Fe(2+) to Fe(3+) without releasing radical oxygen species. It is involved in iro...

Gene Name

CP

Uniprot ID

[P00450](#)

Uniprot Name

Ceruloplasmin

Molecular Weight

122204.45 Da

References

1. Overington JP, Al-Lazikani B, Hopkins AL: How many drug targets are there? *Nat Rev Drug Discov.* 2006 Dec;5(12):993-6. [[PubMed:17139284](#)]
2. Imming P, Sinning C, Meyer A: Drugs, their targets and the nature and number of drug targets. *Nat Rev Drug Discov.* 2006 Oct;5(10):821-34. [[PubMed:17016423](#)]

7. Prothrombin

Kind

Protein

**Pharmacological action**

Unknown

General Function

Thrombospondin receptor activity

Specific Function

Thrombin, which cleaves bonds after Arg and Lys, converts fibrinogen to fibrin and activates factors V, VII, VIII, XIII, and, in complex with thrombomodulin, protein C. Functions in blood homeostas...

Gene Name

F2

Uniprot ID[P00734](#)**Uniprot Name**

Prothrombin

Molecular Weight

70036.295 Da

References

1. Omar MN, Shouk TA, Khaleq MA: Activity of blood coagulation and fibrinolysis during and after hydroxyethyl starch (HES) colloidal volume replacement. Clin Biochem. 1999 Jun;32(4):269-74. [[PubMed:10463819](#)]
2. Cvirn G, Gallistl S, Koestenberger M, Kutschera J, Leschnik B, Muntean W: Alpha 2-macroglobulin enhances prothrombin activation and thrombin potential by inhibiting the anticoagulant protein C/protein S system in cord and adult plasma. Thromb Res. 2002 Mar 1;105(5):433-9. [[PubMed:12062545](#)]
3. Gruber A, Cantwell AM, Di Cera E, Hanson SR: The thrombin mutant W215A/E217A shows safe and potent anticoagulant and antithrombotic effects in vivo. J Biol Chem. 2002 Aug 2;277(31):27581-4. Epub 2002 Jun 17. [[PubMed:12070133](#)]
4. Conway EM, Van de Wouwer M, Pollefeyt S, Jurk K, Van Aken H, De Vriese A, Weitz JI, Weiler H, Hellings PW, Schaeffer P, Herbert JM, Collen D, Theilmeier G: The lectin-like domain of thrombomodulin confers protection from neutrophil-mediated tissue damage by suppressing adhesion molecule expression via nuclear factor kappaB and mitogen-activated protein kinase pathways. J Exp Med. 2002 Sep 2;196(5):565-77. [[PubMed:12208873](#)]
5. Levi M, De Jonge E, van der Poll T: Recombinant human activated protein C (Xigris). Int J Clin Pract. 2002 Sep;56(7):542-5. [[PubMed:12296618](#)]

8. Platelet factor 4**Kind**

Protein

Organism

Human

Pharmacological action

Unknown

General Function

Heparin binding

Specific Function

Released during platelet aggregation. Neutralizes the anticoagulant effect of heparin because it binds more strongly to heparin than to the chondroitin-4-sulfate chains of the carrier molecule. Che...