Drugs

Danaparoid

Targets (1)

IDENTIFICATION

Name	Danaparoid
Accession Number	DB06754
Type	Small Molecule
Groups	Approved, Withdrawn
Description	Danaparoid is a low-molecular-weight heparinoid with an average molecular weight of 5500 Daltons consisting of a mixture of glycosaminoglycans [2]. The active constituents are heparan, dermatan and Chondroitin sulfate [4], and they are isolated from the porcine intestinal mucosa [Label]. Danaparoid possesses a potent antithrombic activity that works by inhibiting activated factor X (Factor Xa) and activated factor II (Factor IIa). It is chemically distinct from heparin by containing different protein binding properties, thus has lower cross-reactivity in heparin-intolerant patients. Danaproid is used in the treatment of heparin-induced thrombocytopenia (HIT) as an off-label indication and prevention of post-operative deep venous thrombosis (DVT). While it was initially approved by the FDA as Orgaran™, danaparoid was withdrawn by Organon International on August 14, 2002, due to a shortage in drug substance by the manufacturer. The use of Orgaran™ was discontinued in the United States however it is available in several other countries including European countries and Japan. Danaparoid sodium is the common salt form in therapeutic preparations and is typically administered subcutaneously.
Synonyms	Not Available

Product Ingredients

INGREDIENT	UNII	CAS	INCHI KEY
Danaparoid sodium	5004UU3156	Not Available	Not applicable

Prescription Products

Show 10 entries Search

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END	
Orgaran	Solution	750 unit	Intravenous; Subcutaneous	Aspen Pharmacare Canada Inc.	1995-12-31	Not applicable	

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Categories

- Agents causing hyperkalemia
- Anticoagulants
- Blood and Blood Forming Organs
- Carbohydrates
- Cardiovascular Agents
- Chondroitin
- Fibrin Modulating Agents
- Fibrinolytic Agents
- Glycosaminoglycans
- Hematologic Agents
- Heparin and similars
- Heparinoids
- Polysaccharides

UNII	BI6GY4U9CW
CAS number	308068-55-5
Weight	Not Available

Chemical Formula	Not Available

InChI	Not Available
IUPAC Name	Not Available
SMILES	Not Available

PHARMACOLOGY

Indication

Indicated for the prophylaxis of post-operative deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing elective hip replacement surgery [Label].

Associated Conditions

Deep Vein Thrombosis caused by Major Abdominal Surgery

Deep Vein Thrombosis caused by Orthopedic Surgery

Deep Vein Thrombosis caused by Thoracic Surgery

Cardiac surgery, heparin-induced thrombocytopenia and thrombosis syndrome

Non-hemorrhagic stroke

Pharmacodynamics

Danaparoid contains a mixture of heparan sulfate, dermatan sulfate and chondroitin sulfate in amounts of approximately 84%, 12% and 4%, respectively [3]. Danaparoid is as an antithrombotic agent that prevents the formation of fibrin in the coagulation pathway. It has a high antifactor Xa to antifactor IIa (thrombin) activity that primarily works via antithrombin III-mediated inhibition of factor Xa [3]. The ratio of antifactor Xa to antifactor II activity is ≥ 20:1 [3]. Danaparoid has a minor effect on platelet function and aggregation [Label]. In a worldwide compassionate-use programme involving a total of 667 patients with heparin-induced thrombocytopenia (HIT), treatment with danaparoid resulted in 93% of successful outcomes in resolving HIT [3].

In healthy volunteers, danaparoid caused significantly less prolongation o f the activated partial thromboplastin time (APTT) and was associated with a significantly lower thrombin time than unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) [3]. Danaparoid displays lower lipolytic activity than UFH *in vitro* and in healthy individuals, leading to lower plasma levels of free fatty acids [3]. Danaparoid has been associated with the cross-reactivity with pathogenic heparin-induced platelet-factor 4 (PF4) antibodies, which occurs in about 10 % or more by *in vitro* testing [1]. The clinical relevance of this effect is not fully understood [1].

Mechanism of action

In the coagulation cascade leading to clot formation, factor X and factor II requires activation to promote subsequent conversion of fibrinogen to fibrin. The mechanism of action of danaparoid resulting in anticoagulant and antithrombic effects involves a complex interaction between 2 components, factor IIa and in particular, factor Xa [3]. Via binding to antithrombin and inducing a conformational change [A32579], danaparoid enhances and catalyzes the the binding of factor Xa to antithrombin, which induces antithrombin-mediated inactivation of factor Xa. This leads to inhibition of thrombin generation and subsequently, thrombus formation [2]. Danaparoid also weakly enhances antithrombin III and heparin cofactor II inactivation of factor IIa [2]. There is evidence that danaparoid also suppresses the activation of factor IX which, in conjunction with simultaneous inhibition of factor X, may lead to antithrombic effects [3].

TARGET	ACTIONS	ORGANISM
(A) Antithrombin-III	positive allosteric modulator	Humans

Absorption

Pharmacokinetic studies on danaparoid are based on the kinetics of its anticoagulant activities, which are mostly antifactor Xa and antifactor IIa activities. The bioavailability of danaparoid is 100% following subcutaneous administration [Label]. Following administration of single subcutaneous doses of 750, 1500, 2250, and 3250 anti-Xa units of danaparoid, the peak plasma anti-Xa activities were 102.4, 206.1, 283.9, and 403.4 mU/mL, respectively [Label]. The time to reach maximum anti-Xa activity is approximately 2-5 hours [Label].

Volume of distribution	Pharmacokinetic studies on danaparoid are based on the kinetics of its anticoagulant activities, which are mostly anti factor Xa and anti factor IIa activities. The volumes of distribution of anti-Xa

Protein binding	Not Available
Metabolism	There is no evidence of hepatic metabolism and danaparoid is unlikely to undergo cellular metabolism [3].
Route of elimination	Renal excretion is the main route of elimination, accounting for approximately 40-50% of the total clearance of antifactor Xa activity following intravenous administration of danaparoid [2]. Therefore in patients with severe renal impairment, the elimination half-life of anti-Xa activity may be prolonged [Label].
Half life	Pharmacokinetic studies on danaparoid are based on the kinetics of its anticoagulant activities, which are mostly anti factor Xa and anti factor IIa activities. The elimination half-life ranges from 19.2 to 24.5 hours during anti-Xa activity and ranges from 1.8 to 4.3 hours during anti-IIa activity [3].
Clearance	Pharmacokinetic studies on danaparoid are based on the kinetics of its anticoagulant activities, which are mostly anti factor Xa and anti factor IIa activities. Total plasma clearance is about 0.36 L/h during anti-Xa activity, which may be accelerated with higher body surface area [Label]. Total plasma clearance during anti-IIa activity ranges from 2.3 to 3 L [3].
Toxicity	Subcutaneous administration of a single dose at 3800 anti-Xa units/kg, which is 20.5 times the recommended dose for humans based on body surface area, was found to be lethal to female rats. Lethal effects were seen in male rats when administering a single subcutaneous dose at 15200 anti-Xa units/kg, which is approximately 82 times the recommended human dose based on body surface area [Label]. In rats, the symptoms of acute toxicity following intravenous administration included respiratory depression, prostration and twitching [Label]. Accidental overdosage of danaparoid may lead to severe bleeding complications. While protamine sulfate may partially neutralize the anti-Xa actions of danaparoid, there is no evidence that it is capable of reducing severe non-surgical bleeding during treatment of danaparoid. In case of serious bleeding, danaparoid should be discontinued and blood transfusions should be administered if necessary. Withdrawal of danaparoid is expected to restore the coagulation balance without rebound phenomenon [Label]. There is no evidence of danaparoid to have a potential to induce carcinogenesis, mutagenesis and impairment of fertility [Label].
Affected organisms	Not Available
Pathways	Not Available
Pharmacogenomic Effects/ADRs	Not Available

INTERACTIONS

Drug Interactions

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

Show 10 entries Search

DRUG	INTERACTION
(1,2,6,7-3H)Testosterone	The therapeutic efficacy of Danaparoid can be increased when used in combination with (1,2,6,7-3H)Testosterone.

DRUG	INTERACTION
(R)-warfarin	The risk or severity of bleeding can be increased when Danaparoid is combined with (S)-Warfarin.
1-(3-Mercapto-2-Methyl-Propionyl)-Pyrrolidine-2-Carboxylic Acid	The risk or severity of hyperkalemia can be increased when 1-(3-Mercapto-2-Methyl-Propionyl)-Pyrrolidine-2-Carboxylic Acid is combined with Danaparoid.
1-Testosterone	The therapeutic efficacy of Danaparoid can be increased when used in combination with 1-Testosterone.
18-methyl-19-nortestosterone	The therapeutic efficacy of Danaparoid can be increased when used in combination with 18-methyl-19-nortestosterone.
3,5-diiodothyropropionic acid	3,5-diiodothyropropionic acid may increase the anticoagulant activities of Danaparoid.
4-hydroxycoumarin	The risk or severity of bleeding can be increased when Danaparoid is combined with 4-hydroxycoumarin.
4-Hydroxytestosterone	The therapeutic efficacy of Danaparoid can be increased when used in combination with 4-Hydroxytestosterone.
5beta-dihydrotestosterone	The therapeutic efficacy of Danaparoid can be increased when used in combination with 5beta-dihydrotestosterone.

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Food Interactions Not Available

REFERENCES

General References

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2. Ibbotson T, Perry CM: Danaparoid: a review of its use in thromboembolic and coagulation disorders. Drugs. 2002;62(15):2283-314. [PubMed:12381232]
3. Wilde MI, Markham A: Danaparoid. A review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. Drugs. 1997 Dec;54(6):903-24. [PubMed:9421696]
4. 24. (2012). In Rang and Dale's Pharmacology (7th ed., pp. 299-300). Edinburgh: Elsevier/Churchill Livingstone. [ISBN:978-0-7020-3471-8]

External Links

PubChem Substance	347910366
Wikipedia	Danaparoid

ATC Codes

B01AB09 — Danaparoid
- B01AB — Heparin group
- B01A — ANTITHROMBOTIC AGENTS
- B01 — ANTITHROMBOTIC AGENTS
- B — BLOOD AND BLOOD FORMING ORGANS

AHFS Codes 20:12.04.16 — Heparins

FDA label Download (566 KB)

CLINICAL TRIALS

Clinical Trials Show 10 entries Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
3	Not Yet Recruiting	Treatment	Cardiac surgery, heparin-induced thrombocytopenia and thrombosis syndrome	1
Not Available	Completed	Not Available	Acute HIT II (Heparin-induced Thrombocytopenia Type II)	1

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Drugs

Manufacturers	Not Available
Packagers	Not Available

Dosage forms

Show 10 entries Search

FORM	ROUTE	STRENGTH
Solution	Intravenous; Subcutaneous	750 unit

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Prices	Not Available
Patents	Not Available

PROPERTIES

State	Solid
Experimental Properties	Not Available
Predicted Properties	Not Available
Predicted ADMET features	Not Available

SPECTRA

Mass Spec (NIST)	Not Available
Spectra	Not Available

TAXONOMY

Classification	Not classified

TARGETS

1. Antithrombin-III

Details

Kind	Protein
Organism	Humans
Pharmacological action	Yes
Actions	Positive allosteric modulator
General Function	Serine-type endopeptidase inhibitor activity
Specific Function	Most important serine protease inhibitor in plasma that regulates the blood coagulation cascade. AT-III inhibits thrombin, matriptase-3/TMPRSS7, as well as factors IXa, Xa and XIa. Its inhibitory a...

Gene Name	SERPINC1
Uniprot ID	P01008

Molecular Weight	52601.935 Da

References

1. Liu J, Pedersen LC: Anticoagulant heparan sulfate: structural specificity and biosynthesis. Appl Microbiol Biotechnol. 2007 Feb;74(2):263-72. doi: 10.1007/s00253-006-0722-x. Epub 2006 Nov 28. [PubMed:17131147]

Drug created on September 14, 2010 10:20 / Updated on April 16, 2019 18:48

This project is supported by the **Canadian Institutes of Health Research** (award #111062), **Alberta Innovates - Health Solutions**, and by **The Metabolomics Innovation Centre (TMIC)**, a nationally-funded research and core facility that supports a wide range of cutting-edge metabolomic studies. TMIC is funded by **Genome Alberta**, **Genome British Columbia**, and **Genome Canada**, a not-for-profit organization that is leading Canada's national genomics strategy with funding from the federal government. Maintenance, support, and commercial licensing is provided by **OMx Personal Health Analytics, Inc.** Designed by **Educe Design & Innovation Inc.**