CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-430/S-003

Final Printed Labeling

ORGARAN® (danaparoid sodium) Injection

Manufactured by Organon Inc.

West Orange, NJ 07052

5310150 7/2001

ORGARAN®

(danaparoid sodium) Injection

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patient should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS, Hemorrhage** and **PRECAUTIONS, Drug Interactions**).

DESCRIPTION

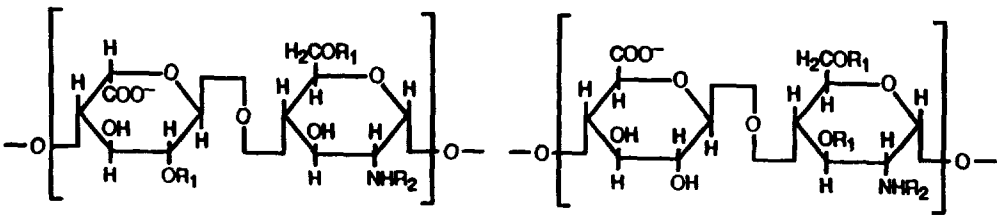
ORGARAN® (danaparoid sodium) Injection is a sterile, glycosaminoglycuronan antithrombotic agent. The active components of ORGARAN®, isolated from porcine intestinal mucosa, are heparan sulfate (~84%), dermatan sulfate (~12%) and a small amount of chondroitin sulfate

(~4%). The average molecular weight is approximately 5500 Daltons.

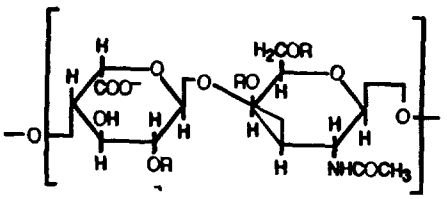
ORGARAN® is intended for subcutaneous injection. Each prefilled syringe or ampule contains 750 anti-Xa units in 0.6 mL solution. ORGARAN® Injection is made isotonic with sodium chloride, adjusted to pH 7 with hydrochloric acid, or sodium hydroxide. ORGARAN® Injection contains 0.15% (w/v) sodium sulfite to prevent discoloration of the solution. The structural formula of the main repeating disaccharide units is as follows:

Structural Formula:

Main Repeating Disaccharide Units:

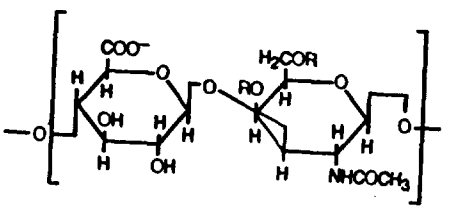


Heparan Sulfate: R_1= H or SO_3^-, R_2= $COCH_3$ or SO_3^-



Dermatan Sulfate

R = H or SO_3^-



Chondroitin Sulfate

CLINICAL PHARMACOLOGY

Pharmacodynamics

Effect on Coagulation Factors

ORGARAN® (danaparoid sodium) Injection is an antithrombotic agent. ORGARAN® prevents fibrin formation in the coagulation pathway via thrombin generation inhibition by anti-Xa and anti-IIa (thrombin) effects. The anti-Xa: anti-IIa activity ratio is greater than 22. Inactivation of factor Xa is mediated by antithrombin-III (AT-III) while factor IIa inactivation is mediated by both AT-III and heparin cofactor II (HC II). ORGARAN® has only minor effect on platelet function and platelet aggregability.

Measurements of Hemostasis

Because of its predominant anti-Xa activity, ORGARAN® has little effect on clotting assays (*e.g.*, prothrombin time [PT], partial thromboplastin time [PTT]). ORGARAN® has minimal effect on fibrinolytic activity and bleeding time.

Pharmacokinetics

The pharmacokinetics of ORGARAN® (danaparoid sodium) Injection have been described by monitoring its biological activity (plasma anti-Xa activity) since no specific chemical assay methods are currently available for the components of ORGARAN®.

By subcutaneous route of administration, ORGARAN® was approximately 100% bioavailable, compared with the same dose administered intravenously. The maximum anti-Xa activity (T_{max}) occurred at approximately two to five hours.

For single subcutaneous doses of 750, 1500, 2250, and 3250 anti-Xa units of ORGARAN® the mean peak plasma anti-Xa activities were 102.4, 206.1, 283.9, and 403.4 mU/mL, respectively. The mean value for the terminal half-life ($T_{1/2}$) was about 24 hours and the clearance was 0.36 L/hour. Clearance was affected by body surface area in that the higher the body surface, the faster the clearance. ORGARAN® is mainly eliminated via the kidneys. In patients with severely impaired renal function, the half-life of elimination of plasma anti-Xa activity may be prolonged, therefore, monitoring such patients carefully is recommended.

Special Populations

Geriatrics

There are insufficient pharmacokinetic data to determine if the absorption, distribution, and elimination of ORGARAN® (danaparoid sodium) Injection are different in elderly (≥65 years) subjects when compared with younger subjects.

Pediatrics

The safety and efficacy of ORGARAN® in pediatric patients have not been established.

Race

There is no information to determine the effect of race on the pharmacokinetics of ORGARAN®.

Hepatic Insufficiency

No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of ORGARAN®.

Renal Insufficiency

No formal studies were conducted to evaluate the effect of renal disease on the disposition of ORGARAN® although ORGARAN® is mainly eliminated by the kidneys. In patients with severely impaired renal function, the half-life of elimination of plasma anti-Xa activity may be prolonged, therefore, careful monitoring of such patients is recommended (see **PRECAUTIONS**).

Drug-Drug Interactions

In clinical studies for the prophylaxis of DVT, no significant drug interactions have been noted in the following drugs: digoxin, cloxacillin, ticarcillin, chlorthalidone, and pentobarbital (see **PRECAUTIONS**).

ORGARAN® should be used with caution in patients receiving oral anticoagulants and/or platelet inhibitors. Monitoring of anticoagulants by Prothrombin Time and Thrombotest is unreliable within 5 hours after ORGARAN® administration (see **PRECAUTIONS**).

Clinical Studies

In a European multicenter double-blind trial, ORGARAN® (danaparoid sodium) Injection was compared with placebo in 196 patients undergoing elective hip replacement surgery. The administration of ORGARAN® for 7 to 14 days post-operatively significantly reduced the overall incidence of DVT to 15% (15/98 patients) compared to the incidence of 57% (56/98 patients) observed with placebo.

Number (%) of Patients with DVT*
Intent-to-Treat

	ORGARAN® N=98	Placebo N=98	p-value[a]
Proximal; N (%)	8 (8)	26 (27)	0.001
Distal; N (%)	14 (14)	51 (52)	<0.001
Overall; N (%)	15 (15)	56 (57)	<0.001

*A patient may be counted more than once (proximal and/or distal)
[a]Using the Cochran Mantel-Haenszel test

In a United States multicenter trial, ORGARAN® was compared with warfarin in 396 patients undergoing elective hip replacement. A significant reduction in the overall incidence of DVT was observed with ORGARAN® (14.6%; 29/199 patients) compared with warfarin (26.9%; 53/197 patients), p=0.003.

Number (%) of Patients with DVT[a]
Intent-to-Treat

	ORGARAN® N=199	Warfarin N=197	p-value[b]
Proximal[c] ; N (%)	3 (1.5)	8 (4.1)	0.13
Distal[d] ; N (%)	28 (14.1)	49 (24.9)	0.007
Overall[e] ; N (%)	29 (14.6)	53 (26.9)	0.003

[a] By positive venogram only
[b] Using the Cochran Mantel-Haenszel test
[c] Popliteal, iliac, and femoral
[d] Calf
[e] A patient may be counted more than once (proximal and distal)

INDICATIONS AND USAGE

ORGARAN® (danaparoid sodium) Injection is 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.

CONTRAINDICATIONS

ORGARAN® (danaparoid sodium) Injection is contraindicated in the following conditions: severe hemorrhagic diathesis, e.g., hemophilia and idiopathic thrombocytopenic purpura; active major bleeding state, including hemorrhagic stroke in the acute phase; hypersensitivity to ORGARAN®; Type II thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibody in the presence of ORGARAN® Injection. ORGARAN® is contraindicated in patients with known hypersensitivity to pork products.

WARNINGS

General

ORGARAN® (danaparoid sodium) Injection is not intended for intramuscular administration. Since a specific standard for the anti-Xa activity of ORGARAN® is used, the anti-Xa unit activity of ORGARAN® is not equivalent to that described for heparin or low molecular weight heparin. Therefore, ORGARAN® cannot be dosed interchangeably (unit for unit) with either heparin or any low molecular weight heparin.

Miscellaneous

ORGARAN® (danaparoid sodium) Injection contains sodium sulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic patients.

Hemorrhage

Hemorrhage can occur at virtually any site in patients receiving ORGARAN® (danaparoid sodium) Injection. An unexplained fall in hematocrit and/or fall in blood pressure should lead to serious consideration of a hemorrhagic event. ORGARAN®, like anticoagulants, should be used with extreme caution in disease states in which there is increased risk of hemorrhage, such as severe uncontrolled hypertension, acute bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, non-hemorrhagic stroke, shortly after brain, spinal or ophthalmological surgery and post-operative indwelling epidural catheter use.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture which can result in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING).

PRECAUTIONS

General

The risks and benefits of ORGARAN® (danaparoid sodium) Injection should be carefully considered before use in patients with severely impaired renal function or hemorrhagic disorders (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests

ORGARAN® (danaparoid sodium) Injection has only a small effect on factor IIa (thrombin)

activity, therefore, when administered at recommended prophylaxis doses, routine coagulation tests (e.g., Prothrombin Time [PT], Activated Partial Thromboplastin Time [APTT], Kaolin Cephalin Clotting Time [KCCT], Whole Blood Clotting Time [WBCT], and Thrombin Time [TT]) are relatively insensitive measures of ORGARAN® activity and, therefore, unsuitable for monitoring.

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with ORGARAN®.

Thrombocytopenia

ORGARAN® (danaparoid sodium) Injection shows a low cross-reactivity with antiplatelet antibodies in individuals with Type II heparin-induced thrombocytopenia. No cases of white clot syndrome or cases of Type II thrombocytopenia have been reported in clinical studies for the prophylaxis of DVT in patients receiving multiple doses of ORGARAN® up to 14 days.

Drug Interactions

In clinical studies for the prophylaxis of DVT, no clinically significant drug interactions have been noted in the following drugs: digoxin, cloxacillin, ticarcillin, chlorthalidone, and pentobarbital.

ORGARAN® (danaparoid sodium) Injection should be used with caution in patients receiving oral anticoagulants and/or platelet inhibitors. Monitoring of anticoagulant activity of oral anticoagulants by Prothrombin Time and Thrombotest is unreliable within 5 hours after ORGARAN® Injection administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term studies in animals have been performed to evaluate the carcinogenic potential of ORGARAN® (danaparoid sodium) Injection. ORGARAN® was not genotoxic in the Ames test, the *in vitro* CHL/HGPRT forward gene mutation assay, the *in vitro* CHO cell chromosome aberration test, the *in vitro* HeLa cell unscheduled DNA synthesis (UDS) test or the *in vivo* mouse micronucleus test. ORGARAN® at intravenous doses of up to 1090 anti-Xa units/kg/day was found to have no effect on fertility or reproductive performance of male and female rats. This dose is 5.9 times the recommended human subcutaneous dose based on body surface area (50 kg body weight and 1.46 m^2 body surface area assumed).

Pregnancy

Teratogenic Effects-Pregnancy Category B

Teratology studies have been performed in pregnant rats at intravenous doses up to 1600 anti-Xa units/kg/day (8.7 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 780 anti-Xa units/kg/day (6 times the recommended human dose based on body surface area) and have not revealed evidence of impaired fertility or harm to the fetus due to ORGARAN® (danaparoid sodium) Injection. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether ORGARAN® (danaparoid sodium) Injection is excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when ORGARAN® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ORGARAN® (danaparoid sodium) Injection in pediatric patients have not been established.

Geriatric Use

Of the total number of patients undergoing elective hip replacement surgery who received ORGARAN® (danaparoid sodium) Injection in clinical studies, 62% (397/645 patients) were ≥65 years and 22% (141/645 patients) were ≥75 years old. No overall differences in safety and effectiveness of ORGARAN® were observed between elderly (≥65 years) subjects and younger subjects. Other reported clinical experience with ORGARAN® has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals to ORGARAN® cannot be ruled out.

ORGARAN® is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The following table summarizes adverse bleeding events that occurred in clinical trials which studied ORGARAN® (danaparoid sodium) Injection compared to placebo, warfarin, and others (heparin, heparin/DHE, acetylsalicylic acid, dextran, and low molecular weight heparins).

Blood Loss and Transfusions
DVT and PE Prophylaxis for Orthopedic Hip Surgery
All Patients Treated

Blood Loss and Transfusions	Total N	ORGARAN®	Placebo	Warfarin	Other[a]
Total (728 Males: 1675 Females)		(n) Mean±SD	(n) Mean±SD	(n) Mean±SD	(n) Mean±SD
Intraoperative Blood Loss(mL)					
Males	596	(330) 694±555	(27) 586±737	(141) 689±499	(98) 754±661
Females	1259	(686) 486±430	(66) 416±252	(219) 471±306	(288) 530±456
Postoperative Blood Loss(mL)					
Males	580	(318) 954±879	(45) 908±812	(88) 817±585	(129) 1056±1055
Females	1256	(639) 700±778	(122) 715±520	(80) 619±352	(415) 798±779
Transfusions (units PRBCs)					
Males	462	(258) 2.6±1.8	(35) 2.7±1.4	(87) 2.5±1.4	(82) 2.9±2.1
Females	1152	(604) 2.6±1.7	(92) 2.8±1.4	(177) 2.1±1.1	(279) 2.8±2.0

[a]"Other" includes the following active reference agents: heparin, heparin/DHE, acetylsalicylic acid, dextran, and low molecular weight heparins.
Total N = Total number of patients with available data across all treatment groups.
n= The number of patients with available data in each respective treatment group and by gender.

Other

The following table summarizes adverse events that occurred at a frequency greater than, or equal to, 2% of patients in clinical trials for the prophylaxis of DVT and PE following elective

hip surgery which studied ORGARAN® (danaparoid sodium) Injection compared to placebo, warfarin, and others (dextran, heparin/DHE, aspirin).

Incidence of Adverse Experiences (≥2%)
DVT and PE Prophylaxis for Elective Hip Surgery
All Patients Treated

Adverse Experience	ORGARAN® N=645 N(%)	Placebo N=135 N(%)	Warfarin N=243 N(%)	Other N=168 N(%)
Fever	143(22.2)	1(0.7)	138(56.8)	3(1.8)
Nausea	92(14.3)	3(2.2)	78(32.1)	8(4.8)
Constipation	73(11.3)	0(0.0)	70(28.8)	2(1.2)
Injection Site Pain	49(7.6)	4(3.0)	0(0.0)	34(20.2)
Rash	31(4.8)	0(0.0)	18(7.4)	2(1.2)
Pruritus	25(3.9)	1(0.7)	14(5.8)	0(0.0)
Peripheral Edema	21(3.3)	0(0.0)	19(7.8)	4(2.4)
Insomnia	20(3.1)	0(0.0)	32(13.2)	0(0.0)
Vomiting	19(2.9)	3(2.2)	20(8.2)	3(1.8)
Joint Disorder	17(2.6)	0(0.0)	15(6.2)	0(0.0)
Headache	17(2.6)	1(0.7)	13(5.3)	0(0.0)
Urinary Tract Infection	17(2.6)	1(0.7)	5(2.1)	5(3.0)
Edema	17(2.6)	0(0.0)	14(5.8)	2(1.2)
Asthenia	15(2.3)	0(0.0)	10(4.1)	1(0.6)
Dizziness	15(2.3)	0(0.0)	14(5.8)	0(0.0)
Anemia	14(2.2)	3(2.2)	5(2.1)	5(3.0)
Urinary Retention	13(2.0)	0(0.0)	14(5.8)	1(0.6)

In addition, the following table summarizes adverse events that occurred at a frequency greater than, or equal to, 2% of patients in clinical trials for the prophylaxis of DVT and PE which

studied ORGARAN® compared to placebo, warfarin, and others (heparin, heparin sodium, heparin calcium, enoxaparin, dalteparin, dextran, heparin/DHE, aspirin).

Incidence of Adverse Experiences (≥2%)
DVT and PE Prophylaxis Indication
All Patients Treated

Adverse Experience	ORGARAN® N=2383 N(%)	Placebo N=276 N(%)	Warfarin N=421 N(%)	Other N=1163 N(%)
Injection Site Pain	327(13.7)	53(19.2)	0(0.0)	153(13.2)
Pain	207(8.7)	0(0.0)	202(48.0)	20(1.7)
Fever	173(7.3)	1(0.4)	150(35.6)	21(1.8)
Nausea	98(4.1)	3(1.1)	79(18.8)	13(1.1)
Urinary Tract Infection	96(4.0)	3(1.1)	27(6.4)	65(5.6)
Constipation	83(3.5)	0(0.0)	73(17.3)	3(0.3)
Rash	51(2.1)	0(0.0)	25(5.9)	5(0.4)
Infection	51(2.1)	3(1.1)	0(0.0)	47(4.0)

OVERDOSAGE

Symptoms/Treatment

Accidental overdosage following administration of ORGARAN® (danaparoid sodium) Injection may lead to bleeding complications. The effects of ORGARAN® on anti-Xa activity cannot be antagonized with any known agent at this time. Although protamine sulfate partially neutralizes the anti-Xa activity of ORGARAN® and can be safely co-administered, there is no evidence that protamine sulfate is capable of reducing severe non-surgical bleeding during treatment with ORGARAN®. In the event of serious bleeding, ORGARAN® should be stopped and blood or blood product transfusions should be administered as needed. Withdrawal of ORGARAN® may

be expected to restore the coagulation balance without rebound phenomenon.

Single subcutaneous doses of ORGARAN® at 3800 anti-Xa units/kg (20.5 times the recommended human dose based on body surface area) and 15200 anti-Xa units/kg (82 times the recommended human dose based on body surface area) were lethal to female and male rats, respectively. Symptoms of acute toxicity after intravenous dosing were respiratory depression, prostration and twitching.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

In patients undergoing hip replacement surgery, the recommended dose of ORGARAN® (danaparoid sodium) Injection is 750 anti-Xa units twice daily administered by subcutaneous injection beginning 1 to 4 hours pre-operatively, and then not sooner than two hours after surgery. Treatment should be continued throughout the period of post-operative care until the risk of deep vein thrombosis has diminished. The average duration of administration in clinical trials was 7 to 10 days, up to 14 days. Patients with serum creatinine ≥2.0 mg/dL should be carefully monitored.

Use in Geriatrics

No overall differences in safety and effectiveness of ORGARAN® (danaparoid sodium) Injection were observed in patients ≥65 years when compared with patients <65 years undergoing elective hip replacement surgery. No dosage adjustments are recommended in elderly patients.

Administration

ORGARAN® (danaparoid sodium) Injection is intended for subcutaneous administration and

should not be administered by intramuscular injection. Subcutaneous injection technique: Patients should be lying down and ORGARAN® Injection administered by deep subcutaneous injection using a fine needle (25 to 26 gauge) to minimize tissue trauma. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held gently between the thumb and forefinger; the skin fold should be held throughout the injection and should neither be pinched nor rubbed afterwards.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

ORGARAN® (danaparoid sodium) Injection is supplied in:

-Ampules containing 0.6 mL (750 anti-Xa units) of danaparoid sodium:
boxes of 10, NDC 0052-0830-11.

-Disposable prefilled syringes containing 0.6 mL (750 anti-Xa units) of danaparoid sodium: boxes of 10, NDC 0052-0830-61. Each ORGARAN® prefilled syringe is affixed with a 25 gauge x 5/8 inch needle.

Storage

-Ampules should be stored at temperatures of 2-30°C (36-86°F).

-Syringes should be stored at a refrigerated temperature of 2-8°C (36-46°F).

-Protect from light.

Rx only

Organon Inc.

West Orange, NJ 07052

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