PRODUCT MONOGRAPH - HIT

PrORGARAN®

Danaparoid Sodium Injection

750 anti-Xa units/ampoule

(1250 anti-Xa units/mL)

Anticoagulant/Antithrombotic Agent

(Heparinoid)

Date of Approval: February 9, 2018

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Control No. 212405

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THERAPEUTIC CLASSIFICATION

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ACTIONS AND CLINICAL PHARMACOLOGY

ORGARAN® (danaparoid sodium) is a mixture of non-heparin low molecular weight sulfated glycosaminoglycuronans derived from porcine intestinal mucosa. Its average molecular weight is 4000-8000 D and the molecular weights of the fractions range from <2000 to >10000 D. ORGARAN® consists of heparan sulfate with low affinity for antithrombin (AT) (about 80%), heparan sulfate with high affinity for AT (about 4%), dermatan sulfate (8-16%) and chondroitin sulfate (<8.5%). ORGARAN® is devoid of heparin or heparin fragments. It has been shown both in animal models and in human studies to possess antithrombotic action.

Compared to heparin, ORGARAN® has a much higher anti-factor Xa/anti-IIa ratio (more than 20:1). Its anti-Xa activity is 11 - 17 U/mg and its anti-IIa activity $\leq$ 0.5 U/mg. ORGARAN® exerts a stronger catalytic effect on the inactivation of factor Xa than on the inactivation of thrombin. The anti-Xa activity is mediated by AT and is not inactivated by endogenous heparin neutralising factors. The anti-thrombin activity is mediated by both AT and heparin cofactor II.

LMW heparins and heparinoids are not measured directly in the bloodstream; instead the effect on clotting mechanisms is measured. ORGARAN® inhibits thrombus formation with approximately the same potency as heparin in animal models but shows greater efficacy at inhibiting extension of pre-formed thrombi. The APTT may not be significantly prolonged

relative to unfractionated heparin. In clinical trials, ORGARAN® showed improved antithrombotic activity when compared to heparin. Both of the heparan sulfate fractions, the high- and low-affinity for AT, contribute to the antithrombotic activity. ORGARAN® has minimal or no effect on platelet function. It produces less bleeding-enhancing activity than heparin in experimental models at equipotent antithrombotic doses. ORGARAN® does not inhibit platelet deposition at therapeutic doses and has only minimal effects on platelet degranulation during hemostatic plug formation. In experimental models, the antithrombotic activity of ORGARAN® is more persistent and the hemorrhagic effects less persistent than those of heparin.

Pharmacokinetics

The absolute bioavailability of danaparoid sodium after subcutaneous administration approaches 100% and the time to reach peak plasma anti-Xa activity levels is approximately 4-5 hours.

The half-lives of elimination of anti-Xa and thrombin generation inhibiting activities are approximately 25 hours and 7 hours respectively, after both subcutaneous and intravenous administration. Steady-state levels of plasma anti-Xa activity are usually reached within 4-5 days of dosing. Measured by thrombin generation inhibiting activity steady-state levels are reached earlier, i.e. within 1-2 days.

ORGARAN® is mainly eliminated by renal excretion and animal experiments indicate that the liver is not involved in its metabolism. In patients with severely impaired renal function the half-life of elimination of plasma anti-factor Xa activity may be prolonged.

INDICATIONS AND CLINICAL USE

ORGARAN® (danaparoid sodium) is indicated for treatment of patients with an acute episode of Heparin-Induced Thrombocytopenia (HIT), and for prophylaxis in patients with a history of HIT.

CONTRAINDICATIONS

ORGARAN® (danaparoid sodium) must not be administered by the intramuscular route or in patients with:

- history of thrombocytopenia and/or thrombosis with ORGARAN®
- severe untreated hypertension
- diabetic or hemorrhagic retinopathy
- hemorrhagic stroke in the acute phase
- uncontrollable active bleeding state
- hypersensitivity to ORGARAN® or any of its components including sulphite

WARNINGS

ORGARAN® (danaparoid sodium) SHOULD BE USED WITH CARE IN PATIENTS WITH HEPATIC INSUFFICIENCY, RENAL INSUFFICIENCY, OR A HISTORY OF GASTROINTESTINAL ULCERATION.

ORGARAN® should not be used in the following cases unless, in the opinion of the physician, the potential benefits outweigh the potential risks:

- patients with active gastric or duodenal ulcer (unless this is the reason for surgery)
- patients with severe hemorrhagic diathesis (unless no alternative antithrombotic treatment is available)
- patients with other conditions or diseases involving an increased risk of hemorrhage or hemorrhagic cerebrovascular accident (except if there are systemic emboli)
- acute or subacute bacterial endocarditis
- major blood clotting disorders
- surgery involving brain, spinal cord, eyes or ears.

Since severe bleeding may occur post-operatively in HIT patients undergoing a cardiopulmonary bypass procedure, ORGARAN® is not recommended during the procedure, unless no other antithrombotic treatment is available.

Determination of anti-factor Xa levels in plasma is the only method available for monitoring danaparoid sodium activity. Anticoagulant activity is characterized by a very flat dose response curve in clotting assays such as prothrombin time, activated partial thromboplastin time, kaolin cephalin clotting time and thrombin clotting time, therefore, these routine clotting assays are unsuitable for monitoring its anticoagulant activity.

Anti-Xa units of ORGARAN® have a different relationship to clinical efficacy than those of heparin and low molecular weight heparins. The plasma anti-Xa activity induced by ORGARAN® is not neutralised by circulating proteins such as PF4 and histidine rich glycoprotein. Also, ORGARAN® has been shown to induce three major biochemical responses in the circulation: anti-Xa activity, anti-thrombin activity and thrombin generation inhibitory activity, all of which have different half-lives following i.v. injection (25 hours, 4 hours, and 7 hours, respectively). Therefore, at different times after the injection of ORGARAN®, different ratios of the various activities will be found and these will have a bearing on the clinical efficacy and safety of ORGARAN®. Thus, there is no clear relationship between anti-Xa units and efficacy.

There is a better relationship to clinical efficacy with the actual dose of ORGARAN® than with the plasma anti-Xa activity since a single dose can result in a range of plasma anti-Xa activity levels. This variation is caused by factors such as time of blood sampling, body weight, body mass index, renal function and other (unknown) factors.

Protamine is not a neutralizing agent for the activity of ORGARAN®. However, in emergency, plasmapheresis has been shown to effectively reduce the plasma anti-Xa levels.

There have been cases of intra-spinal hematomas with the concurrent use of low molecular weight heparins and spinal/epidural anesthesia resulting in transient or permanent paralysis. The risk of these events may be higher with the prolonged use of post-operative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis; nonsteroidal anti-inflammatory drugs (NSAIDS), platelet inhibitors, or other drugs affecting coagulation. The risk is also increased by traumatic or repeated epidural or spinal procedure. Although these effects have until

now not been documented with the concomitant use of ORGARAN® and spinal/epidural anesthesia, the potential risk cannot be ruled out. Therefore, ORGARAN® should only be used concurrently with spinal/epidural anesthesia when the therapeutic benefits to the patients outweigh the possible risks. When used concurrently, no spinal invasion should be performed for 12 hours following the last dose of ORGARAN®, and the next dose should be held until at least 2 hours after the anesthesia procedure. The same rules apply to the withdrawal or manipulation of the catheter. Careful vigilance for neurological signs is recommended with rapid diagnosis and treatment, if signs occur. See also Adverse Reactions.

The dose of ORGARAN® for DVT prophylaxis in HIT patients needs to be individualized and possibly decreased for those with moderate to severe renal failure. ORGARAN® should be carefully monitored in patients with severely impaired renal function because the main route of elimination is via the kidney. The half-life for anti-Xa activity in patients with impaired renal function is longer than for people with normal renal function (29-35 hours in patients with renal impairment vs. 25 hours in normal patients). In studies with renal failure patients, it was observed that the individual pharmacokinetics of plasma anti-Xa effect is not readily predictable and may show widely different patterns of inter-patient variability. For patients presenting with HIT who have to undergo renal hemodialysis or hemofiltration a specially designed dosage schedule is available, see Dosage and Administration. In patients undergoing repeated dialysis procedures, the predialysis bolus is suitably adjusted to prevent accumulation of the plasma anti-Xa activity. In patients undergoing chronic renal hemodialysis there is no need for additional DVT prophylactic dosing, since the drug's antithrombotic effect persists between dialyses.

Except under special circumstances ORGARAN® should not be used when abortion is imminent or threatened. It may be used in such cases only when, in the opinion of the physician, the increased risk of bleeding is outweighed by the risk of thrombosis and thrombo-embolism.

ORGARAN® contains sodium sulphite, which may cause allergic reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown. Sulphite sensitivity is seen more frequently in asthmatics than in non-asthmatics.

Use in Patients with Prosthetic Heart Valves

ORGARAN® should not be used to prevent thromboembolism in patients with prosthetic heart valves because there is inadequate data to assess the safety and effectiveness in these patients. Adequate studies have not been completed to establish the conditions of use (e.g., the dosage). There have been cases of thrombosis in aortic and mitral prosthetic valves, some of which have resulted in death. (See also Use in Pregnancy).

Use in Pregnancy and Lactation and for Children**.**

Animal studies have not demonstrated any teratogenic effects or placental transfer of ORGARAN®. The use of ORGARAN® in pregnancy has been studied in a small number of subjects. Observations in 23 pregnant women (13 in the first, 4 in the second and 6 in the third trimester), of whom 13 had HIT and the remainder other types of heparin intolerance, have so far given no indication that the use of ORGARAN® during pregnancy leads to fetal abnormalities or to exacerbation of bleeding in mother or infant during delivery. In the few cases in which umbilical cord blood was tested for the presence of anti-Xa activity, no anti-Xa activity was found.

There has been no experience with ORGARAN® during human lactation. Mothers receiving ORGARAN® should avoid breast-feeding. Based on the paucity of data it is advised, in general, that ORGARAN® should not be used during pregnancy and lactation in women with HIT unless no alternative anti-thrombotic treatment is available and the therapeutic benefits to the patients outweigh the possible risks.

Pediatric experience with ORGARAN® is very limited. The use of ORGARAN® should take place in consultation with a coagulation expert, and has to be based on plasma anti-Xa levels (see Dosage and Administration).

ORGARAN® should not be used to prevent thromboembolism in pregnant women with prosthetic heart valves, **unless the patient has HIT**. There has been very limited use of ORGARAN® in this patient population for the management of HIT Type II. In patients treated with LMW heparins, clots have developed that resulted in blockage of the valve and death. There is

inadequate data to ascertain the safety, effectiveness or dosage in pregnant women with prosthetic heart valves.

Use in Knee Surgery

The risk of bleeding in knee surgery patients receiving LMW heparins or heparinoids such as ORGARAN® may be greater than in other orthopedic surgical procedures. It should be noted that hemarthrosis is a serious complication of knee surgery. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin or heparinoid in this patient population.

PRECAUTIONS

Clinical Diagnosis of HIT

HIT can present in various ways some of which are common to other disorders. The most compelling diagnosis should be the clinical one. The following factors have all been recognised as possible or confirmatory diagnostic features of HIT:

- development of thrombocytopenia or platelet count drop of >40% within 5-15 days of starting heparin use;
- development of heparin resistance, i.e. the need for increasing doses to prevent extension of, or new, thromboses or to maintain the desired APTT;
- exclusion of other causes for this (extent of) platelet count reduction, e.g. surgery, drugs, sepsis, DIC;
- platelet count rises after stopping all heparin use (including small flush doses to maintain the patency of intravascular catheters etc, which are often ignored or overlooked). The rise may be slow or delayed if other reasons for platelet count suppression are present with HIT;
- observation of an (inadvertent) rechallenge platelet count reduction when heparin is re-introduced (especially following repeated dialyses);
- a new acute thrombo-embolic event (which may show as a white, platelet-rich clot at embolectomy) has occurred, either within the vascular system or in an artificial system, e.g. graft or dialyser.

HIT can also present in other clinical guises, e.g. heparin-induced skin necrosis, transient global amnesia, acute systemic reactions to an injection etc. The occurrence of these or the last two points above can be considered as clinical confirmation of HIT.

The initial diagnosis of HIT, based upon clinical observations, may be augmented by additional laboratory investigations such as immediately repeating the platelet count, examining a blood film for platelet clumping, or identifying platelet-derived microparticles using flow cytometry. Although used in the past, the detection of high levels of immunoglobulins on the platelet surface is both insensitive and non-specific for the diagnosis of HIT. Whenever possible, attempts should be made to detect the heparin-induced antibody (or its equivalent if a chemically related antithrombotic glycosaminoglycuronan (GAG) has been used). A number of tests are available for this. All have a very high positive predictive value, but their sensitivity for the antibody, and hence the level of false negative tests, varies. These tests are the following, listed in order of their diagnostic accuracy:

a. SRA (serotonin release test/assay). Although generally regarded as the "golden standard" it does not lend itself to routine use since it depends upon the release of ^{14}C-labelled serotonin from pre-loaded platelets, and it requires a license to use radioactive isotopes.

b. HIPA (heparin-induced platelet activation) test. It is a more sensitive (lower detection limit for the antibody) modification of the routine platelet aggregation test (PAT, see below). The HIPA test compares favourably with the SRA. It should be noted that in the USA some investigators use the abbreviation HIPA when they are actually referring to the PAT.

c. ELISA (enzyme-linked immunosorbant assay), which is available in kit form, is relatively simple to perform in any laboratory. It is sensitive and able to distinguish IgG, IgM and IgA antibodies and hence to provide further insight into the pathophysiology of HIT. However, it is based upon an initial binding step involving PF4, a protein derived from the platelet, which increases the specificity of the test. This protein binds strongly to heparin (and *in vivo* this complex is the target of the antibody responsible for the clinical picture of HIT), but has limited or no binding to LMWHs or ORGARAN® (danaparoid sodium), respectively.

d. PAT (platelet aggregation test). Although less sensitive than the other methods for detecting the heparin-induced antibody, it is the most widely used test. Unlike the SRA, HIPA and ELISA tests it does not require special reagents or equipment.

In some patients, even if available, a test on the first plasma sample may not be diagnostic because either interfering levels of heparin are present or the antibody concentration is too low or both. If the antibody titre is too low, this will produce false negatives with the less sensitive functional tests. Therefore, patients with clinically suspected, serologically negative HIT should have a repeat blood sample drawn 24 hours later for a retest. Interference from other plasma proteins will affect all tests particularly the ELISA. This can usually be overcome by preheating the serum to 60°C for 30 minutes. The antibody may not be induced by the usual heparin:PF4 complex but by interaction of heparin with other proteins (e.g. IL-8 or NAP2) which may produce false negative results.

In stroke patients, intracranial/intracerebral hemorrhage (hemorrhagic stroke) should be excluded by CT scan or MRI prior to the administration of ORGARAN®.

Biochemical Monitoring

ORGARAN® has only a moderate prolonging effect on clotting time assays such as APTT or thrombin time. For laboratory monitoring of effect, plasma anti-Xa activity using amidolytic methods are recommended. For all assay methods, ORGARAN® should be used as the calibrator for the reference standard. Dose increases aimed at prolonging APTT to the same extent as with unfractionated heparin could cause overdose and bleeding.

ORGARAN® is administered subcutaneously or intravenously. With subcutaneous administration, the individual patient's antifactor Xa activity level will not remain within the range that would be expected with unfractionated heparin by continuous i.v. infusion throughout the entire dosing interval. The peak plasma antifactor Xa level occurs 4 hours after subcutaneous administration. Administration of single doses of up to 3200 U ORGARAN® produce levels of less than 0.5 U/mL anti-Xa activity. Steady-state plasma anti-Xa levels are reached at day 4-5, but can be reached earlier with the subcutaneous dosing schedule if an i.v. bolus is given as a loading dose. ORGARAN® administered as an i.v. bolus dose of 4000-4800 U produces mean anti-Xa levels of greater than 0.5 U/mL. ORGARAN® should be administered as directed in the Dosage and Administration Section.

Patient Monitoring

As with all antithrombotic agents, there is a risk of systemic bleeding with ORGARAN® administration.

After treatment is initiated, patients should be carefully monitored for bleeding complications. This may be done by regular physical examination of patients, close observation of the surgical drain and periodic measurements of hemoglobin, and anti-factor Xa determinations. Bleeding complications may be considered major if hemoglobin is decreased by 2 g/dL or if a transfusion of 2 or more units has been required. With normal prophylactic doses, ORGARAN® does not modify global clotting tests of activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin clotting time (TT). Therefore, treatment cannot be monitored with these tests.

Measurement of the Quick, INR, PT may not be reliable within the first 5 hours of an Orgaran injection. Since the INR depends on PT and/or TT, this cannot be measured accurately within the first 5 hours of the overlap of OAC's and ORGARAN®

ORGARAN® is administered subcutaneously or intravenously. Following subcutaneous administration, the individual patient's anti-factor Xa activity level will not remain within the range that would be expected with unfractionated heparin by continuous i.v. infusion throughout the entire dosing interval. Mean plasma anti-Xa levels, measured 10 minutes after a single i.v. injection of 1500-1600 U, 3000-3200 U or 6400 U were as follows: 0.4, 0.9 and 1.6 anti-Xa U/mL, respectively. When ORGARAN® was administered at steady-state in doses of 800, 1600, 2400 and 3200 U, anti-Xa levels 5 minutes after injection were found to be 0.3, 0.58, 1.07 and 1.14 U/mL, respectively. Pharmacokinetic analysis shows linearity of the kinetics of anti-Xa effect after multiple i.v. bolus injections. (See also Biochemical Monitoring). ORGARAN® should be administered as directed in the Dosage and Administration section.

Platelets

Platelet counts should be determined prior to commencement of therapy with ORGARAN® and, subsequently, every other day during the first week, twice a week during the two weeks thereafter, and after three weeks once a week.

Caution is recommended when administering ORGARAN® to patients with congenital or drug induced (other than heparin) thrombocytopenia, or platelet defects.

Cross-reactivity in Heparin-induced Thrombocytopenia Patients

The clinical implications of serological cross-reactivity testing in HIT patients are unclear. ORGARAN® has been used as an alternative anticoagulant in patients who had developed thrombocytopenia with heparin. In HIT patients tested for initial therapy, the cross-reactivity with ORGARAN® (<10%) was lower than with LMW heparins (>90%).

Repeated use of ORGARAN® in 34 patients on 2 or more well separated occasions has not led to sensitization during the repeat uses. If HIT is suspected or confirmed all sources of heparin or LMWH, if the causative agent, must be eliminated.

Although the most certain test for HIT is a positive re-challenge platelet thrombocytopenia, the danger of inducing a serious thromboembolic event prohibits deliberate use in that manner. Reliance upon laboratory demonstration of heparin-induced platelet hypersensitivity or direct assay of the antibody with ORGARAN® is necessary. Testing for cross-reactivity with ORGARAN® is strongly advised if clinical suspicion of cross-reactivity arises. If confirmed then ORGARAN® should never again be used in that patient.

Apart from problems of interference with detection of the heparin-induced antibody, inherent, to some extent, in all of the serological tests, residual heparin in the plasma sample of a patient with suspected HIT may cause confusion. This is because the “blanks/controls” will also react positive during cross-reactivity testing. There are ways of absorbing out this heparin, but the specific antibody can also be lost by this procedure, thereby reducing the sensitivity of the test. Cross-reactivity testing of the heparin-induced antibody with alternative GAGs should be performed whenever the tests discussed above are available. However, the ELISA test is possibly less reliable in this respect because if the compound being tested binds poorly or not at all to PF4, then cross-reactivity testing may be impaired. The clinical implications of serological cross-reactivity in HIT patients are unclear. ORGARAN® has been successfully used as an alternative anticoagulant in HIT patients with positive serological cross-reactivity testing.

The following salient points should be considered when evaluating platelet sensitivity testing in HIT patients but are not the only ones:

1. A negative platelet test in an acutely thrombocytopenic patient does not rule out a positive in vivo reaction.
2. A positive cross-reactivity test on a pre-treatment blood sample should not preclude careful use of ORGARAN® if other heparin alternatives are unavailable. Accordingly, frequent examination for signs of clinical cross-reactivity should be instituted.
3. Samples taken a few months, or later, after a thrombocytopenic reaction may test negative for cross-reactivity because the antibody has disappeared. However, commencement of ORGARAN® treatment may induce the production of cross-reaction antibody, with the accompanying risk of thrombocytopenia.
4. Use of a sensitizing agent that resulted in a positive HIT test in the past is not recommended even for a single occasion
5. If clinical cross-reactivity with ORGARAN® is suspected it should be immediately discontinued, because a fatal outcome with ORGARAN® has been reported.

Antithrombotic Treatment Initiation

Due to limitations with laboratory testing and its interpretation, it is unnecessary to await a negative result before beginning ORGARAN® treatment. However, careful clinical and platelet count monitoring (see above) is necessary to detect the earliest signs of clinical cross-reactivity. Treatment should be changed immediately if cross-reactivity is suspected. Cross-reactivity may manifest clinically as renewed or unresponsive platelet count reduction, a new or extension of a pre-existing thrombotic event, skin necrosis and rarely bleeding. However, although important to stop ORGARAN® immediately, serological confirmation must be performed to help put into perspective other possible causes of these events. For example, sepsis, DIC, other drugs or diseases are associated with thrombocytopenia. Hemostatic factor deficiency, inappropriately low dose of ORGARAN®, heparin or warfarin co-administration, anti-phospholipid syndrome/SLE may result in thrombotic events. Warfarin or heparin co-administration may cause skin necrosis. Inappropriately high doses of ORGARAN®, warfarin or heparin co-administration may lead to bleeding. If cross-reactivity testing with ORGARAN® is negative and

these other possibilities are considered to be the cause of the problem then ORGARAN® can be restarted. Inappropriate dosing with ORGARAN® has successfully responded to appropriate dosage adjustment.

Selection of General Surgery Patients: Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, age 60 years or above.

Elderly. Age is highly correlated to risk of thrombosis. No increased bleeding tendency has been observed in the clinical studies with ORGARAN® in elderly patients with normal kidney and liver function. No dose reduction should be necessary unless kidney or liver function is severely impaired.

DRUG INTERACTIONS

In clinical studies no clinically significant interactions of ORGARAN® with other medications have been found. In general, combination with antithrombotics that act by other mechanisms such as oral anticoagulants or ASA would be additive. ORGARAN® may be used together with oral anticoagulants or drugs which interfere with platelet function, such as aspirin and non-steroidal anti-inflammatory drugs, but caution remains necessary. Monitoring of anticoagulant activity of oral anticoagulants by prothrombin time and Thrombotest is unreliable within 5 hours after ORGARAN® administration.

The interaction of ORGARAN® with the following drugs has been studied. All effects on kinetic parameters mentioned below are considered of no clinical relevance. No clinically relevant effects have been observed on biochemical, hematological and urinary parameters.

Aspirin	no effects on hemostasis.
Acenocoumarol	slight decrease in anti-Xa clearance.
Cloxacillin	slight increase in elimination half-life of anti-Xa activity.

Ticarcillin	slight increase in anti-Xa clearance.
Digoxin	slight increase in anti-Xa clearance; slight decrease in digoxin area under the curve of plasma concentration versus time.
Chlorthalidone	slight decrease in anti-Xa clearance and central volume of distribution.
Pentobarbital	decrease of anti-IIa clearance.
Antipyrine	no significant effect on cytochrome P-450 system.

Since most patients treated with ORGARAN® are severely ill, often with multiple disorders, many receive a wide variety of co-medications. Many patients have received concomitant antithrombotics, the two most important of which are oral anticoagulants and thrombolytics. Such patients have been treated on average with 4-5 drugs other than antithrombotics. Most were antibiotics, anti-hypertensives, diuretics, anti-diabetics, cardiac stimulants and analgesics. Anti-cancer or immuno-suppressive drugs have also been used frequently and have been associated with delayed platelet count recovery. Despite this variety there is no evidence of any direct interaction with ORGARAN®. Occasionally it has been considered by the investigators that some drugs contribute independently to the suppression of, and possibly to delay in recovery of, the platelet count.

ORGARAN® is intended primarily for subcutaneous and intravenous use. When administered as an intravenous bolus or infusion, it should be given separately and not mixed with other drugs. However, ORGARAN® is compatible with, and therefore, can be added to, the following infusions: normal saline, dextrose/saline, Ringer's or Lactated Ringer's and mannitol. In these solutions it remains stable for up to 48 hours at room temperature.

There is no antidote for ORGARAN® overdose. Protamine is not a neutralising agent for the activity of ORGARAN®. In cases of surgically uncontrollable severe bleeding, plasmapheresis has been used to reduce the circulating levels of ORGARAN®, see Symptoms and Treatment of Overdosage.

ADVERSE REACTIONS

Adverse reactions experienced in HIT patients have not differed from those of non-HIT patients receiving ORGARAN® (danaparoid sodium).

Bleeding

As with any antithrombotic treatment, hemorrhagic manifestations can occur. Injection site hematomas are a common side effect with ORGARAN® occurring at a frequency of 5% or less.

Whereas bleeding is an inherent risk with all antithrombotic therapy, no increased risk of bleeding was found during the operative and postoperative periods (based on volume of blood loss and the number of units of packed red blood cells transfused) when ORGARAN® 750 anti-Xa units s.c. bid administered before and after surgery was compared with placebo or active treatments (such as unfractionated heparin, warfarin and dextran). Plasma anti-Xa activity levels have not correlated with bleeding complications during ORGARAN® therapy, although hemorrhage has been more frequent with higher doses such as those used with HIT patients. Until further data are available, midinterval anti-Xa concentrations greater than 0.5 units/mL should be avoided during post-operative prophylaxis of thromboembolism. Risk factors associated with bleeding on therapy with heparins and heparinoids include a serious concurrent illness, surgical and accidental trauma, chronic heavy alcohol consumption, use of platelet inhibiting drugs other than aspirin or NSAID's and severe renal failure. Bleeding may range from minor local hematomas to major hemorrhage. The early signs of bleeding may include epistaxis, hematuria, or melena, although these can also occur after severe bleeding has started. Bleeding may occur at any site and may be difficult to detect; such as retroperitoneal bleeding.

There have been cases of intra-spinal hematomas with the concurrent use of low molecular weight heparins and spinal/epidural anesthesia especially if the spinal tap has been traumatic. It can result in transient or permanent paralysis (incidence of 1:45,000). See also Warnings.

Liver

Changes in plasma transaminases (AST, ALT and alkaline phosphatase) have been observed with ORGARAN®. No clinical significance has been demonstrated because the patients involved were severely ill. In general there is no concordance in the changes in plasma enzyme levels suggesting a specific effect on the liver or any other source of these enzymes (muscle [cardiac, skeletal, uterine etc], erythrocyte or kidney). Nevertheless, transient elevations of transaminases

(AST and ALT) are a consistent finding with all members of the LMWH class, as well as with unfractionated heparin. The mechanism associated with the increased levels of transaminases has not been elucidated and no consistent irreversible liver damage has been observed.

Hypersensitivity

Thrombocytopenia, skin rash, and allergic reactions are rare, but occur with all LMW heparins and heparinoids. ORGARAN® should be discontinued in patients showing primary local or systemic allergic responses. Occasionally in patients with injection site reactions to heparin these recur with ORGARAN®, but with decreasing severity and may then disappear despite continued ORGARAN® administration. If antibody-induced thrombocytopenia occurs, the use of ORGARAN® should be stopped and the cause determined. If due to ORGARAN®, then alternative treatment should be considered.

Anaphylactoid reactions to unfractionated heparin and the low molecular weight heparins have been rarely observed. Heparin, ancrod and warfarin- induced necrosis has occurred with LMWH's but has not been observed with ORGARAN®.

Skeletal

No osteoporosis was observed in rats or dogs after 6 months of treatment with high intravenous doses of ORGARAN®. Similarly, no osteopenic effects have been reported, even in patients treated for over 3 months, including 12 pregnancies (particularly vulnerable to this side effect of heparin). However, since this symptom has been reported as an adverse effect after long term treatment with unfractionated heparin at high doses, the risk of osteoporosis cannot be excluded.

Lipid metabolism

Compared to unfractionated heparin, ORGARAN® induces a smaller release of lipoprotein lipase and hepatic triglyceride lipase. The total lipase release by ORGARAN® is less than 20% that of equivalent antithrombotic doses of unfractionated heparin. The lipoprotein lipase response is reduced by half and the hepatic triglyceride lipase response is reduced even further.

The following table lists adverse events observed in clinical trials, in which ORGARAN® was given for DVT and PE Prophylaxis in Orthopedic Hip Surgery [daily dosage range: 500 U s.c. qd - continuous i.v. infusion of 183 U/hour], DVT and PE Prophylaxis (without Orthopedic Hip Surgery) and Treatment [daily dosage range: 375 U s.c. qd - 2000 U bid], Management of Acute or Progressing Ischemic Stroke [daily dosage range: 625 U i.v. - 9600 U/day (given as 2400 U 4 hours after bolus, 4800 U after 12 hrs, 2400 U after 8 hours)], Hemodialysis [daily dosage range: 500 U - 6000 U i.v. bolus], Cardiac Catheterization [daily dosage range: 3200 U i.a.] or for other Clinical Pharmacology studies [daily dosage range: 100 U - 6400 U i.v.]. It should be noted that placebo was only used for a limited number of clinical situations, and that the ratio of peri-operative to medical uses was much higher in the Orgaran® treated patients. This probably explains most of the differences in frequency of the events listed.

These adverse events are listed irrespective of causality by ORGARAN®, the disease state being treated, other concomitant diseases, concomitant medications or other unknown reasons.

Table 1 - Incidence of Adverse Experiences (>1%) by Body System and Treatment

Body System Adverse Experience	**Orgaran** n=4478 (%)	**Placebo** n=310 (%)
Body as a Whole		
Fever	212 (4.7)	1 (0.3)
Infection	68 (1.5)	3 (1.0)
Injection site pain	351 (7.8)	53 (17.1)
Pain	218 (4.9)	0 (0.0)
Pyrexia	78 (1.7)	0 (0.0)
Digestive System		
Constipation	86 (1.9)	0 (0.0)
Nausea	116 (2.6)	3 (1.0)
Vomiting	41 (0.9)	3 (1.0)
Hemic & Lymphatic System		
Anemia	15 (0.3)	3 (1.0)
Leukocytosis	44 (1.0)	2 (0.6)
Metabolic & Nutritional Disorders		
Hypoproteinemia	42 (0.9)	4 (1.3)
Respiratory System		
Pneumonia	46 (1.0)	2 (0.6)

Skin & Appendages		
Rash	45 (1.0)	0 (0.0)
Urogenital System		
Urinary Retention	46 (1.0)	0 (0.0)
Urinary Tract Infection	105 (2.3)	3 (1.7)

Notes: A patient may have been counted in more than one body system and in more than one AE within a body system. This table does not include adverse experiences with a COSTART term of "Death". Those AEs with an incidence of <1% are not listed in this table.

In addition to the adverse effects listed in the table, other events have been observed in surgery, non-surgery and miscellaneous patients. Some examples were: bruise, hematoma, hemorrhage, urine abnormal, hematuria, urinary tract bleed (microscopic), atrial fibrillation, partial loss of consciousness, urinary incontinence, involuntary muscle contractions, tremor, decreased arterial pressure, restlessness, apnoea, fatigue, urinary tract bleeding, hypotension, increased alkaline phosphate, peripheral edema, confusion, insomnia, asthma, thrombocytopenia, sepsis, cerebral infarction, cerebral hemorrhage, thrombosis venous deep, hemiparesis. These events are listed regardless of causality and have not necessarily been attributed to ORGARAN®.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Hemorrhage is the major clinical sign of overdosage. In case of accidental overdosage, the routine hematological count and other coagulation parameters should be measured. Minor bleeding rarely requires specific therapy, and reducing or delaying subsequent doses of ORGARAN® (danaparoid sodium) is usually sufficient. ORGARAN® should be discontinued or temporarily interrupted (with subsequent continuance at a lower dose) in cases of major bleeding. Transfusion with fresh frozen plasma, or if bleeding is uncontrollable, plasmapheresis or surgery should be considered. Protamine is not a neutralizing agent for the activity of ORGARAN®.

DOSAGE AND ADMINISTRATION

ORGARAN® (danaparoid sodium) is expressed in U (anti-Xa units)/mL as opposed to IU/mL (as for unfractionated heparin and most of the low molecular weight heparins). These units of measurement are not interchangeable and there is no conversion factor to convert from one to the other.

Plasma anti-Xa activity is linearly related to the dose of ORGARAN® given. If it is necessary to monitor anticoagulant activity, e.g. if the patient is very small or very large (outside the range of 55-90 kg) or in patients with acute renal failure, and for individual dose setting, a functional anti-factor Xa activity assay using a chromogenic peptide substrate should be used. For the results of this assay ORGARAN® must be used to construct the standard curve.

In patients with severely impaired renal function (Creatinine levels ≥ 220 μmol) the second and subsequent doses of ORGARAN® may have to be reduced because the half-life of plasma anti-factor Xa activity may be prolonged. The dosage may require adjustments in order to keep the anti-Xa levels similar to those in normal patients. ORGARAN® should be used with caution and the plasma anti-Xa activity monitored in case of accumulation. At steady-state (3-4 days after initiation of therapy), consistent plasma levels of > 0.5 anti-Xa units are indicative of accumulation and, therefore, suggest that dosage should be decreased or temporarily withdrawn. In patients with end-stage renal failure requiring hemodialysis, pre-dialysis doses for the third and subsequent procedures are reduced according to a recommended schedule (see the following table) to avoid accumulation. To achieve this regular pre-dialysis monitoring of the plasma anti-Xa activity is recommended. For dosing in children during renal dialysis see below under Pediatric Treatment.

<u>Treatment or prevention in current or past episodes of HIT, with or without thrombotic events</u>
If HIT is suspected or confirmed, all heparin must be discontinued immediately (including flush doses to maintain patency of vascular access and lines) and the need for further anticoagulation assessed.

Although the predictive value of in vitro cross-reactivity to HIT-associated antibodies has been queried, it is currently recommended that cross-reactivity should be excluded, when possible, before initiation of ORGARAN® therapy.

HIT is such a serious side effect of heparin and the LMWH because it presents a very high risk for thrombo-embolic events which may be fatal. Hence, treatment of patients with current HIT, i.e. with circulating antibody, requires augmentation of the usual doses used to prophylax such patients when they do not have HIT. The antibody usually circulates for up to 3 months after

heparin is discontinued. Therefore, in patients who have not had serological confirmation of their HIT this is a safe limit for considering HIT as current. Past HIT patients, i.e. those beyond this 3 month interval since heparin discontinuation can be considered free of antibody and hence their risk for thrombosis is no different from other patients who have not had HIT. It must be noted that for patients who have had a prior incidence of thrombosis, the risk of developing another thrombotic event is greater. Therefore, an increased dose of ORGARAN® may be required. Since the dosing schedules for ORGARAN® in current HIT patients have been shown to be safe, as well as efficacious, then the same dosing regimens can be used for past HIT patients requiring similar prophylaxis or treatment of thrombo-embolism.

Recommended dosage regimens of ORGARAN® in patients with HIT are presented in Table 2; recommendations take into account underlying diseases and coexistent hemostatic disorders.

Table 2 - Recommended ORGARAN® Dosage Regimens for Adults with Heparin-induced Thrombocytopenia (HIT) who Require further Anticoagulation

Reason for further anticoagulation	Patient characteristics/type of procedure	Body weight (kg)	Dosage (antifactor Xa units) [duration]	Expected plasma antifactor Xa levels (U/L)
DVT prophylaxis	Current HIT	≤90	750 bid or tid sc [7-10 days] For rapid attainment of prophylaxis levels, an initial i.v. bolus of 1250 can be given	200 (on day 1), 200-400 (day 5,6h after morning dose) Plasma levels of 400 should not be exceeded. Steady-state is expected after 4-5 days of therapy
		> 90	1250 bid or tid sc [7-10 days] For rapid attainment of prophylaxis levels, an initial i.v. bolus of 1250 can be given	
	Past HIT (>3 months)	≤90	750 bid or tid sc [7-10 days]	200 (on day 1), 150-400 (day 5, 6h after morning dose)
		>90	1250 bid or 750 tid sc [7-10 days]	
Established DVT or pulmonary embolism	Thrombosis <5 days old	55-90	2250-2500 i.v. bolus* then 400/h [4h] then 300/h [4h] then 150-200/h [5-7 days] (or maintenance of 2000 sc bid for 4-7 days).	500-700 (5-10 min after bolus), <1000 (during adjustment phase), 500-800 (during maintenance) 400-800 for sc administration
		≤55	1250-1500 i.v. bolus then 400/h [4h] then 300/h [4h] then 150-200/h [5-7 days] or maintenance of 1500 sc bid (for 4-7 days).	
		>90	3750 i.v. bolus then 400/h [4h] then 300/h [4h] then 150-200/h [5-7 days] or maintain with 1750 sc tid (for 4-7 days).	
	Thrombosis ≥5 days old	≤90	1250 i.v. bolus then 750 sc bid or tid	500-700 (5-10 min after i.v. bolus) 300-500 (day 2-3) Plasma levels should not exceed 500 for sc doses. Steady-state is expected after 2-3 days of therapy
		>90	1250 i.v. bolus then 750 sc tid or 1250 sc bid or tid	
Surgical thromboprophylaxis	Nonvascular surgery	≤90	750 sc [1-4h before surgery] repeated ≥ 6h postoperatively then 750 bid sc [7-10 days] (starting the day after surgery)	150-350 (on day 4-5; 6 h after morning dose) Plasma levels should not exceed 350
		>90	750 sc [1-4h before surgery] repeated ≥ 6h postoperatively then 1250 bid sc or 750 tid sc [7-10 days] (starting the day after surgery)	

Reason for further anticoagulation	Patient characteristics/type of procedure	Body weight (kg)	Dosage (antifactor Xa units) [duration]	Expected plasma antifactor Xa levels (U/L)
	Embolectomy	55-90	2250-2500 i.v. bolus before surgery then 1250 bid sc ≥ 6 h postoperatively. Patients may receive 750 bid sc or tid or oral anticoagulants after several days of i.v. therapy	500-700 (5-10 min after bolus), 250-350 (on day 2-3 if started on sc administration postoperatively), 500-800 (on day 2-3 if started on infusion)
		>90	2250-2500 i.v. bolus before surgery then 150-200/h [5-7 days] ≥6h postoperatively. Patients may receive 750 bid sc or tid or oral anticoagulants after several days of i.v. therapy	
Cardiac procedures	Cardiac catheterisation	<90	2500 i.v. bolus before procedure	NS
		>90	3750 i.v. bolus before procedure	
	Percutaneous transluminal coronary angioplasty		2500 i.v. bolus before procedure then 150-200/h immediately postoperatively [1-2 days]. Patients may receive 750 bid or tid sc or oral anticoagulants after several days of i.v. therapy	500-700 (5-10 min after bolus), 500-800 (during infusion)
	Intra-aortic balloon pump catheterisation	<90	2500 i.v. bolus before procedure then 150-200/h postoperatively. If the patient has no other thrombotic complications, ORGARAN® can be given 1250 i.v. bolus (if parenteral anticoagulants were stopped > 24hrs previously) then 750 bid or tid or 1250 bid sc otherwise omit bolus.	500-700 (5-10 min after bolus), 500-800 (during infusion) 300-500 (6 hrs after the previous sc injection of ORGARAN®)
		>90	3750 i.v. bolus before procedure then 150-200/h postoperatively. If the patient has no other thrombotic complications, ORGARAN® can be given 1250 i.v. bolus (if parenteral anticoagulants were stopped > 24hrs previously) then 750 bid or tid or 1250 bid sc otherwise omit bolus.	
Peripheral vascular bypass			2250-2500 i.v. bolus before surgery then 150-200/h ≥ 6 h postoperatively [5-7 days]. Patients may receive 750 bid or tid sc or oral anticoagulants after several days of i.v. therapy	500-700 (5-10 min after bolus), 500-800 (during infusion)
Cardiopulmonary bypass			125/kg body weight i.v. bolus after thoracotomy then 3/mL as priming fluid then 7/kg/h (started at the time of bypass hook-up and stopped 45 min before expected end of bypass). Maintenance of 1250 sc bid or 750 sc tid or infusion of 150-200 U/h (starting 6 hrs after procedure	1500-2000 during by-pass procedure
Hemodialysis	Dialysis every other day or less frequently		3750 i.v. bolus before first 2 hemodialysis then 3000 i.v. bolus (if plasma antifactor Xa levels <300 U/L) or 2500 i.v. bolus (if plasma antifactor Xa levels 300-350) or 2000 i.v. bolus (if plasma antifactor Xa levels 350-400)*	500-800
		<55	2500 i.v. bolus before first 2 hemodialysis then 2000 i.v. bolus(if plasma antifactor Xa levels <300 U/L) or 1500 i.v. bolus (if plasma antifactor Xa levels 300-350) or 1500 i.v. bolus (if plasma antifactor Xa levels 350-400)*	
	Daily dialysis		3750 i.v. bolus before first dialysis then 2500 before second dialysis	500-800
		<55	2500 i.v. bolus before first dialysis then 2000 before second dialysis	
Hemofiltration		55-90	2500 i.v. bolus then 600/h [4h] then 400/h [4h] then 200-600/h to maintain plasma antifactor Xa levels of 500-1000 U/L	500-1000
		<55	2000 i.v. bolus then 400/h [4h] then 150-	

Reason for further anticoagulation	Patient characteristics/type of procedure	Body weight (kg)	Dosage (antifactor Xa units) [duration]	Expected plasma antifactor Xa levels (U/L)
			400/h to maintain plasma antifactor Xa levels of 500-1000 U/L	

*If plasma antifactor Xa levels are >400 U/L, ORGARAN® should not be given before dialysis. However, if fibrin threads appear in the bubble chamber, 1500 antifactor Xa units may be given.
Abbreviations: bid=twice daily; DVT=deep vein thrombosis; i.v. = intravenous; sc= subcutaneous; tid=3 times daily

Conversion to Oral Anticoagulant Use (OAC)

Recent observations suggest that starting OAC's too early in patients with HIT may lead to skin necrosis or thrombotic events, probably due to precipitate reductions in Protein C levels, unless a parenteral anticoagulant is administered at the same time. Thus, OAC therapy should not be initiated until there is adequate anti-thrombotic control with the parenteral drug used to replace heparin.

6. After ORGARAN® 750 U bid sc, OAC's can be started before ORGARAN® is withdrawn to allow the Quick, INR, PT etc. to reach therapeutic levels. This may take up to 5 days, but since after discontinuation of ORGARAN® its effect on plasma anti-Xa continues for 24 h or more, then the patient should be adequately protected for a slightly longer transition period. Measurement of these parameters may not be reliable within 5 h of an ORGARAN® injection.

7. After ORGARAN® 1250 bid sc, OACs can be started but the ORGARAN® dose should be reduced to 750 U bid sc. and the directions followed as in 1 above.

8. OAC's can be given with the i.v. infusion (maximum rate 300 U/h) which can then be stopped when the required INR is reached (maximum 3.0). However, if a bleeding risk is present then either the ORGARAN® regimen should be changed to 1250 U bid, sc and the procedure followed as in 2 above, or the infusion rate should be reduced to 75 U/h with a delay of 24 hours before starting OACs.

9. In HIT patients for whom conversion to OAC's is contraindicated (i.e. pregnant patients and patients on renal dialysis), ORGARAN® has been used chronically for as long as required. It has been used at doses proposed in Table 2, in pregnant patients for up to 26 weeks and in renal dialysis patients for up to 4½ years, without reports of adverse reactions that differed in either frequency or severity from those reported with short term use.

Dosage in the elderly: clearance of anti-factor Xa has not been shown to be markedly reduced in the elderly and the usual dosage is recommended.

Pediatric Treatment - *Acute Thrombosis (arterial and/or venous)*
30 U/kg i.v. bolus injection, then 1.2-4.0 U kg/hr. The expected plasma anti-Xa levels after the i.v. bolus should be 400 - 700 U/L. At steady-state 400- 600 U/L (or 500 - 800 U/L for higher doses).

Prophylaxis - 10 U/kg bid sc.

Renal Dialysis (for the first two dialyses): *< 10 years old* - 30 U/kg +1000 U

10 - 17 years - 30 U/kg + 1500U

(3rd and subsequent dialyses): If pre-dialysis plasma anti-Xa level > 500 U/L, then no ORGARAN® required for next dialysis. If 300-500 U/L > then reduce the total dose by 250 U. If < 300 U/L then give previous dialysis dose.

Flush Doses for Catheter Patency
ORGARAN® can be used intermittently to maintain the patency of i.v. lines/catheters, and/ or access ports thereof, if saline flushes do not work adequately. For this purpose one ampoule of 750 U (0.6 mL) can be diluted in 50 mL saline and 5-10 mL used to flush each line/port etc. as required.

The prophylactic treatment of patients with ORGARAN® does not preclude the use of other modalities of prophylaxis (see under Drug Interactions).

For information on monitoring of patients, please refer to PRECAUTIONS - Biochemical Monitoring and Clinical Monitoring.

PHARMACEUTICAL INFORMATION

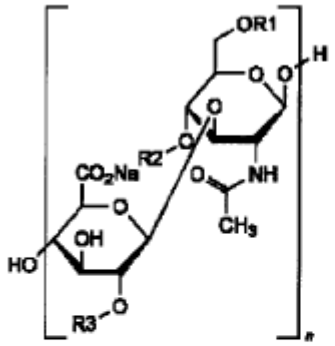
Drug Substance

Chemical (USAN) Name	Danaparoid sodium	
Molecular Formula	N/A	
Molecular Weight	fraction ≤ 2000 D:	≤ 13%
	fraction ≤ 4000 D:	≤ 39%
	fraction 4000-8000 D:	≥ 50%
	fraction ≥ 8000 D:	≤ 19%
	fraction ≥ 10000 D:	≤ 11%
Physical Form	White to almost-white, powder.	
Solubility	Water: more than 200 mg/mL at 20°C.	
Melting Point	N/A	

Description: Danaparoid sodium is a mixture of straight chain mucopolysaccharides (sulphated glycosaminoglycuronans) comprising of heparan sulphate, dermatan sulphate and a minor amount of chondroitin sulphate derived from porcine mucosa. Heparan sulphate with low affinity for AT makes up approximately 80%, heparan sulphate with high affinity for AT (about) 4%, dermatan sulphate 8-16% and chondroitin sulphate less than 8.5%. In addition, the heparan fraction with high affinity for AT contains a pentasaccharide fragment with molecular homology to the AT binding sequence observed in heparin (see chemical structure).

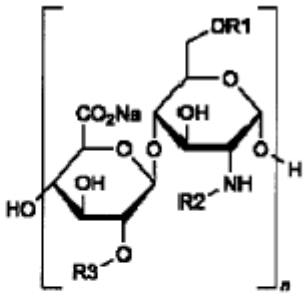
Structural Formula and Chemistry

Chondroitin sulfate family



ΔDI	R1	R2	R3
-OS	H	H	H
-6S	SO_3Na	H	H
-4S	H	SO_3Na	H
-US	H	H	SO_3Na
-(U,6)S	SO_3Na	H	SO_3Na
-(U,4)S	H	SO_3Na	SO_3Na
-(4,6)S	SO_3Na	SO_3Na	H
-(U,4,6)S	SO_3Na	SO_3Na	SO_3Na

Heparan sulfate family



ΔDiHS	R1	R2	R3
-OS	H	Ac	H
-6S	SO_3Na	Ac	H
-NS	H	SO_3Na	H
-US	H	Ac	SO_3Na
-(U,N)S	H	SO_3Na	SO_3Na
-(6,N)S	SO_3Na	SO_3Na	H
-(U,N,6)S	SO_3Na	SO_3Na	SO_3Na

Dosage Form

Composition

Each ampoule contains: 0.6 mL danaparoid sodium (750 anti-Xa units); sodium sulphite 0.9 mg; sodium chloride to isotonic; hydrochloric acid to pH 7.0; water for injection to 0.6 mL. The anti-Xa unit is derived from the international heparin standard in an antithrombin-III containing buffer system.

Stability and Storage Recommendations

Store at 2 - 30°C. Protect from light.

AVAILABILITY OF DOSAGE FORM

ORGARAN® (danaparoid sodium) is supplied in 1-mL glass ampoules. Each ampoule contains 750 anti-factor Xa units danaparoid sodium (1250 anti-factor Xa units/mL). It is a sterile, isotonic solution of pH 7 in water for injection and is suitable for subcutaneous and intravenous injection.

PHARMACOLOGY

Effect on coagulation

The main effect of danaparoid sodium is the inhibition of factor Xa and, in contrast to heparin, it is not affected by the heparin neutralising activity of plasma. Danaparoid sodium has a much smaller effect on IIa inhibition with a ratio Xa/IIa inhibition of > 20:1 measured immediately after i.v. injection. Both the anti-IIa and anti-Xa effects contribute to the inhibition of thrombin generation. Danaparoid sodium does not alter the plasma levels of AT-III, Factors II, VII, X, and fibrinogen indicating that the influence on coagulation is not mediated via effects on clotting factor levels. As such, the mode of action of danaparoid sodium on the coagulation system differs from that of heparin and oral anticoagulants.

Effective inhibition of thrombin-induced conversion of fibrinogen to fibrin has been demonstrated in studies involving patients undergoing routine hemodialysis and cardiac catheterisation, which have shown sustained suppression of plasma fibrinogen peptide A (FPA) release following a bolus injection of ORGARAN® (danaparoid sodium).

Effect on fibrinolysis

Danaparoid sodium appears to have no effect on the fibrinolytic system. No effect was shown on plasma levels of plasminogen, tissue plasminogen activator and on α_2-antiplasmin. No fibrin degradation products Fragments E and $B\beta_{15-42}$ were formed and no effect was observed on euglobulin clot lysis.

Effects on platelets

In contrast to heparin, danaparoid sodium displays a much lower propensity to induce thrombocytopenia, does not change plasma levels of β-thromboglobulin, platelet factor 4 and thromboxane B_2; danaparoid sodium also fails to induce spontaneous aggregation of platelets and has no effect on threshold aggregating levels of various agonists for platelet aggregation. Thrombin-induced aggregation is inhibited due to the anti-IIa activity of danaparoid sodium.

Bleeding time and platelet plug formation

Danaparoid sodium showed no or only a small prolongation of the bleeding time in studies using increased template pressure. In studies where heparin showed a prolongation of the bleeding time, the effect of danaparoid sodium was always much smaller.

Pharmacokinetics

Pharmacokinetic studies have primarily been based on the kinetics of relevant anticoagulant activities of danaparoid sodium, because no specific chemical assay methods are available. In animal models the time courses of the long-lasting anti-Xa and antithrombotic activities of danaparoid sodium were strongly related.

In humans (healthy male and female volunteers including some elderly) kinetic parameters of anti-Xa, anti-IIa, IIaGI-activity and pharmacokinetics of the LA-fraction are summarized in the following table. The total number of subjects studied (n) includes both i.v. and s.c. administration.

	n	$t_{1/2abs.}$ (h)	$t_{1/2distr.}$ (h)	$t_{1/2elim.}$ (h)	V (l)		clearance (l/h)
					central	total	
anti-Xa	79	2.0±0.7 (n=20)	3.1±0.8	24.5±9.6	4.0±0.7	9.1±2.2	0.4±0.1
anti-IIa	52	not determined	1.0±0.8 (n=28)	4.3±3.5	6.2±2.5 (n=28)	9.0±3.1	2.3±1.2
IIaGI	20	3.6±0.6 (n=4)	0.5±0.3	6.7±3.2	5.0±1.4	17.2±6.9	2.9±1.1
LA-fract.	12	2.0±0.6	0.4±0.2	3.5±2.1	5.0±1.6	14.6±5.6	4.7±1.3

The absolute bioavailability of danaparoid sodium after subcutaneous administration approaches 100% and the time to reach peak plasma anti-Xa activity levels is approximately 4-5 hours.

The half-lives of elimination of anti-Xa and thrombin generation inhibiting activities are approximately 25 hours and 7 hours respectively, after both subcutaneous and intravenous

administration. Steady-state levels of plasma anti-Xa activity are usually reached within 4-5 days of dosing. Measured by thrombin generation inhibiting activity steady-state levels are reached earlier, i.e. within 1-2 days.

Danaparoid sodium is mainly eliminated by renal excretion and animal experiments indicate that the liver is not involved in its metabolism. In patients with severely impaired renal function the half-life of elimination of plasma anti-factor Xa activity may be prolonged.

TOXICOLOGY

Acute toxicity

Intravenous administration of danaparoid sodium to rats and dogs resulted in LD_{50} values of 3800 anti-Xa U/kg and greater than 28000 anti-Xa U/kg, respectively. Clinical symptoms observed were bradypnoea, twitching and prostration in the rat and prolonged bleeding at the injection site, hematoma and swelling of the treated limb in the dog.

Clinical symptoms observed in rats administered danaparoid sodium s.c. included eye-blanching, hematoma at the site of injection, extensive hemorrhages and pale visceral organs with an LD_{50} of 15200 anti-Xa U/kg.

Repeated dose toxicity

No direct systemic effects were induced following intravenous doses up to 1520 anti-Xa U/kg in rats for 2 weeks, whereas increased liver weight without any accompanying toxic manifestations, cardiac and locomotion disturbances were observed in dogs. These effects in dogs occurred in addition to the expected effects due to the pharmacological activity of danaparoid sodium.

Daily i.v. administration of 200, 800, and 3200 anti-Xa U/kg for 6 weeks did not induce any sign of toxicity in rats or dogs. All effects observed were due to post-hemorrhagic anemia syndrome which resulted in the termination of one female dog in the medium and high dose groups. These effects were completely reversible in all surviving animals.

Chronic i.v. administration of 100, 400, and 1600 anti-Xa U/kg danaparoid sodium to rats for 6 months, followed by a 4-week recovery period resulted in no gross or microscopic findings attributable to danaparoid sodium. However, daily administration of 100, 400, and 1600 anti-Xa U/kg to dogs for 6 months with a 4 week recovery period resulted in several deaths. One mid-dose male died in week 24 due to hemothorax, one male and 2 females in the high-dose group were sacrificed due to excessive blood loss on days 12, 53, and 56, respectively. Three males and 2 females in the high-dose group were sacrificed due to deteriorating health after 10 weeks of treatment. Treatment was discontinued in the remaining 2 males and females in this group. The low and mid-dose groups completed the full 6 months of treatment. A treatment-related hyperplasia of the bone marrow occurred in this group, however, disappeared following the recovery period. Post-hemorrhagic anemia syndrome was mainly noted in the high dose group due to the exaggerated pharmacological activity of danaparoid sodium. Danaparoid sodium did not induce direct systemic adverse effects.

Daily doses of up to 1520 anti-Xa U/kg (400 mg/kg) s.c. for 2 weeks did not induce direct systemic adverse effects in rats, but caused excessive hemorrhage at the site of injection, especially in the high dose group. Hematomas resulting in post-hemorrhagic anemia syndrome were induced in dogs at these doses and it was concluded that daily doses should not exceed 200 mg/kg in these animals.

Subcutaneous administration of daily doses of 160, 640, and 1600 anti-Xa U/kg for 6 weeks did not induce direct systemic adverse effects in rats, although 1 of 8 females in the intermediate group, 1 of 8 males and 4 of 8 females in the high dose group died during treatment. Death was due to post-hemorrhagic anemia syndrome which was found to be reversible following the post-dosing period in all surviving animals. Daily s.c. doses of 160, 480 and 1600 anti-Xa U/kg for 6 weeks in dogs did not induce any direct systemic adverse effects, although 2 of 5 females and 2 of 5 males in the intermediate dose group and 3 of 4 females and 3 of 4 males in the high dose group were killed prematurely or died spontaneously due to post-hemorrhagic anemia syndrome. Again, this syndrome was found to be reversible in all surviving animals.

Fetal toxicity

Intravenous administration of danaparoid sodium to pregnant rabbits during days 6-18 of gestation at daily doses of 280, 470, and 780 anti-Xa U/kg did not induce toxicity and had no affect on maternal food consumption and body weight. No increase in post-implantation loss was observed and no teratogenicity induced.

Fertility studies

Danaparoid sodium was administered intravenously at daily doses of 390, 650, and 1090 anti-Xa U/kg to sexually mature female rats for 2 weeks prior to mating, during the mating period and pregnancy, and for 4 weeks of lactation. Equivalent doses were also administered intravenously to sexually mature male rats for 9 weeks prior to mating and during the mating period. General condition, behaviour mating performance and fertility were not adversely affected in either case.

No significant increase of embryotoxic or teratogenic effects were observed. Fifty percent of the pregnant females were allowed to deliver and their untreated F_1-offspring were mated within the same dose group with no adverse effects exerted upon fertility of the offspring.

Mutagenic potential

Danaparoid sodium tested at doses up to 80 anti-Xa U/plate showed no mutagenic potential in the AMES test, test for gene mutation in Chinese hamster V79 cells, test for unscheduled DNA synthesis in HeLa S3 cells and chromosome aberrations in Chinese hamster ovary cells. Intravenous administration of up to 12500 anti-Xa U/kg danaparoid sodium to Swiss CD-1 mice did not induce micronuclei in polychromatic erythrocytes.

Local tolerance

Intravenous administration of danaparoid sodium at daily doses of 3200 anti-Xa U/kg for 2 weeks in rats did not elicit local side effects. No direct local effects were seen after s.c. administration of daily doses of 1600 anti-Xa U/kg. Subcutaneous hemorrhages were seen at the site of injection which were attributable to the pharmacological properties of danaparoid sodium.

CLINICAL TRIALS

The following table demonstrates the reduction in the frequency of DVT observed during ORGARAN® (danaparoid sodium) prophylactic treatment compared to active and placebo control treatments in seven major efficacy studies. These studies included 860 patients receiving ORGARAN®, 702 on active control and 134 on placebo control. Of the patients receiving ORGARAN®, 263 had elective hip replacement, 245 were operated upon for hip fracture, 257 underwent general surgery and 95 were non-hemorrhagic stroke patients.

Clinical Indication	Control treatment	Risk reduction	
		total	proximal
Elective hip surgery	Placebo	73%	72%
Elective hip surgery	Heparin/DHE	46%	26%
Fractured hip surgery	Dextran	62%	40%
Fractured hip surgery	Warfarin	58%	74%
General surgery	Heparin	29%	47%
Non-hemorrhagic stroke	Placebo	86%	100%
Non-hemorrhagic stroke	Heparin	71%	63%

Data represents percentage risk reductions with respect to control treatment both for total and proximal DVT

In both of the elective hip trials, ORGARAN® reduced the incidence of DVT compared to control treatments. The incidence of DVT in patients undergoing elective hip surgery was reduced from 57% in the placebo group to 15% in the ORGARAN® group ($p \leq 0.01$) and from 32% in the heparin/DHE (5000 IU) group to 17% in the ORGARAN® group ($p \leq 0.05$).

In patients undergoing surgery for fractured hip, the incidence of DVT was significantly less following ORGARAN® treatment than in the dextran group (13% vs 35%, $p \leq 0.001$). ORGARAN® was also superior to warfarin in reduction of DVT incidence (6.5% vs 15.3%, $p=0.051$, 6.5% vs 19.4%, $p=0.008$, 7.5% vs 19.4%, $p=0.017$) over 3 study periods, days 1-7, 1-10, and 1-14, respectively.

The incidence of DVT decreased to 11.8% following ORGARAN® as compared to 16.6% following heparin in patients undergoing general surgery. This difference was not statistically significant.

ORGARAN® has been evaluated for the prevention of DVT in patients with acute ischemic stroke in two Canadian studies. A double-blind study involving 75 patients with non-hemorrhagic stroke and lower limb paralysis resulted in an incidence of 4% DVT in the ORGARAN® group as compared to 28% in the placebo group (p=0.005). The corresponding rates for proximal DVT were 0% and 16%, respectively (p=0.01). In a second double-blind, randomized trial, ORGARAN® (n=45) was compared with unfractionated heparin (n=42) in the prevention of DVT. DVT resulted in 9% of ORGARAN®-treated patients and in 31% of the unfractionated heparin group (p=0.014). The corresponding rates for proximal DVT were 4.4 and 11.9% respectively (p=0.255).

ORGARAN® has been used to treat 742 patients with HIT on 793 occasions (including 51 repeat treatment episodes) with overall good clinical results. Of the 742 patients receiving ORGARAN®, 646 had a first time episode of acute HIT, 4 past HIT patients presented with acute HIT as a result of recent heparin re-challenge (total current HIT patients=650). One hundred forty one patients presented with past HIT, but had a need for parenteral antithrombotic therapy. For 2 patients the HIT status (i.e. current or past) is unknown.

In the 51 repeat treatment episodes ORGARAN® was used for more than one course of therapy (2-4 occasions,) in 34 patients. The 793 treatment requests in HIT patients include 13 pregnant patients. In addition, 10 pregnant patients who were intolerant to heparin for other reasons were also treated with ORGARAN®. Treatment initiation was equally distributed between the three trimesters of pregnancy and continued for 1-26 weeks.

ORGARAN® was administered for both the treatment of a thrombo-embolic event and subsequently for prophylaxis, to prevent a new or recurring thrombosis, in 101 of the 793 HIT requests for its use. The continued use of ORGARAN® for prophylaxis was necessary because a persistent bedridden state, and/or the need for surgery and/or an invasive vascular procedure, and/or protection of an extracorporeal circuit, was not possible with other available antithrombotic agents. Thus these 101 patients received at least two different ORGARAN® dosing regimens during their treatment episode.

In total ORGARAN® was used in 407 requests in 393 HIT patients to treat a thrombo-embolic event, and in 487 requests in 463 HIT patients for 548 clinical situations for prophylactic use. For many patients it was used more than once, particularly those undergoing surgery who had several separate operations. The 548 uses for prophylaxis comprise 106 occasions for routine thrombo-prophylaxis, on 76 occasions for an invasive vascular procedure, on 126 occasions (from 1 to multiple dialyses) for extracorporeal circuit protection, for 97 general surgical procedures, for 70 peripheral vascular operations and for 73 operations with cardiopulmonary bypass.

The Treatment outcome in 110 episodes was designated as non-evaluable either because no information was supplied on the treatment outcome (n=57) or the information supplied was inadequate to make a decision concerning the ORGARAN® treatment effect (n=53). Many of the latter patients died or suffered a non-fatal SAE, but the information supplied, despite requests for clarity, did not allow the relationship of the death to HIT, the co-morbid disorder, or the use of ORGARAN® to be distinguished. These fatal and nonfatal events have been included in the various treatment assessment tables. But the non-evaluable outcomes have not been included in the success/failure calculations.

ORGARAN® use was considered successful for the treatment of thrombosis for 94.5% of the evaluable outcomes (342/362) and for all the various prophylaxis uses on 95.4% of the evaluable outcomes.

The overall success rate of evaluable patient outcomes is 94.4% (645/683 treatment episodes). Success being evaluated as lack of abnormal bleeding, increase in platelet count, no new or extension of thrombosis on appropriate doses of ORGARAN®. It was possible to evaluate the global outcome of ORGARAN® use within a treatment request as a failure, if an operation was successful, but the patient suffered an ORGARAN® related serious adverse event (SAE). Hence the slightly lower overall success rate. Thirty eight treatments 38 failed, and 110 were not evaluable. The 38 failures are summarised in Table 5. In 7 of the 38 treatment failures the platelet aggregation test became positive; one suffered thrombo-embolic sequelae and in all the platelet count dropped. Failure was also recorded for thrombo-embolic events with or without a platelet count reduction or a serious bleeding event, all attributed to the ORGARAN® treatment.

Table 3 - ORGARAN® Treatment Failures

Total No.[5]	Lab.[1] Test	Clinical Complication			No. Died
		PCR[2]	TE[3]	MB[4]	
1	0	+	+	-	0
5	+	+	-	-	1
1	+	-	-	+	0
1	-	+	+	-	0
1	-	+	-	-	0
1	-	-	+	-	0
6	ND	+	+	-	4
3	ND	+	-	+	3
7	ND	+	-	-	3
8	ND	-	+	-	3
4	ND	-	-	+	2
38	7	24	17	8	16

[1] Serological test for cross-reactivity
[2] Platelet count reduction
[3] Thrombo-embolic event
[4] Major bleed
[5] Of patients in the row

Data on cross-reactivity development (initial or sero-conversion) during exposure to ORGARAN® in HIT patients is limited. Of 315 HIT patients, who were tested for cross reactivity before ORGARAN® treatment commenced, 7 were initially positive but received ORGARAN®. Of the remaining 308 patients with negative serological tests, 5 sero-converted during ORGARAN® treatment. A further 3 patients were found to have positive tests as a result of clinical evidence of cross-reactivity developing during ORGARAN® use, but they had not been tested before treatment commenced. The time course and frequency of antibody induction by ORGARAN® in HIT patients is unknown. Among the 5 patients known to have developed sero-conversion during ORGARAN® therapy 4 developed a platelet count reduction only and the 5th, in addition suffered a thrombotic event. However, 5 of the 7 patients with positive cross-reactivity before treatment were successfully treated without mishap for between 9 and 42 days. Some patients have shown persistent or renewed thrombocytopenia, and occasionally life-threatening thrombotic events despite negative serological tests, however, these were

occasionally associated with co-morbid disorders with a high thrombotic risk, e.g. cancer, DIC, severe sepsis, anti-phospholipid syndrome etc.

No cross-reactivity occurred in the 34 patients who received more than 1 course of ORGARAN®. Thus the estimated frequency of cross-reactivity during ORGARAN® re-exposure cannot be calculated.

These results, involving a broad variety of clinical settings (often in association with severe co-morbid pathology), the lower cross-reactivity rate with the heparin-induced antibody (<10% using routine test methods) compared with that of the low molecular weight heparins (>90%) and the low rate of seroconversion, suggest that ORGARAN® may be an acceptable alternative treatment for patients who suffer from HIT and who require anticoagulation.

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