Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Orgaran 750 anti-Xa units/0.6ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Orgaran contains danaparoid sodium, which is a non-heparin mixture of low molecular weight sulfated glycosaminoglycuronans derived from animal musoca, comprising heparan sulfate, dermatan sulfate and minor amount of chondroitin sulfates. One ampoule (0.6 mL) contains 750 anti-factor Xa units danaparoid sodium corresponding to 1250 anti-factor Xa units per mL. The anti-Xa unit is derived from the international heparin standard in an antithrombin containing buffer system.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear/colorless to pale yellow aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a. Prevention and treatment of thrombo-embolic disorders in patients who require urgent parenteral anticoagulation because of the development or a history of heparin-induced thrombocytopenia (HIT).

b. Prevention of deep vein thrombosis (DVT) and its possible consequences, in particular in patients undergoing orthopaedic, major abdominal or thoracic surgery.

4.2 Posology and method of administration

a. HIT-patients
With respect to this therapeutic indication a number of dosing schedules is available, depending on the underlying disease and the accompanying hemostatic defects.
Plasma anti-Xa activity is linearly related to the dose of Orgaran given. In general, monitoring of plasma anti-Xa activity is not necessary. However, in patients suffering from renal insufficiency and/or patients >90 kg body weight monitoring, once or twice a week during routine subcutaneous or intravenous therapy, is recommended to check for drug accumulation or under dosing, respectively.If monitoring of anticoagulant activity is performed then a functional anti-factor Xa test using a specific chromogenic peptide substrate should be used. In this test Orgaran should be used as the standard for constructing the reference curve.

•*Prevention of thrombo-embolism:*
In patients with heparin-induced thrombocytopenia (HIT) without thrombo-embolism (i.e. isolated HIT) dose recommendations depend on the thrombotic risk.
In patients with past HIT (>3 months before the present admission) dose recommendations are the same as for patients without HIT.

In patients with acute HIT (≤ 3 months), i.e. with circulating (LMW)heparin-induced antiplatelet antibody, higher daily dosages are necessary: 2250-3750 anti-Xa units subcutaneously, divided over three doses (8 hourly), administered for 7-10 days, unless it is required longer in patients for whom there is no reasonable antithrombotic alternative. When choosing the dosing regimen, body weight and occurrence of bleeding should be considered.
In general, a loading intravenous bolus injection given at the same time and equal to the first subcutaneous divided dose is recommended. If the bleeding risk is high or the patient is actively bleeding, or the patient has recently been given a dose of heparin or low molecular weight heparin then the loading intravenous bolus should be omitted. For patients without an increased bleeding risk the intravenous infusion regimen (see under 'Treatment of thrombo-embolic disorders or prevention of thrombosis during continuous renal replacement therapy') is an alternative, especially if untreated for more than 24 hours or

Doppler/compression ultrasound examination of the limbs reveals a covert (sub-clinical) thrombo-embolic event.
The intended plasma anti-Xa activity levels should not go above 0.8 anti-Xa units/mL at steady-state. In patients who are actively bleeding, unless it is the reason for surgical intervention, the intended plasma anti-Xa levels should not go above 0.4 anti-Xa units/mL at steady-state.
•*Treatment of thrombo-embolic disorders or prevention of thrombosis during continuous renal replacement therapy:*
2250 anti-Xa units (for patients <55 kg body weight 1500 anti-Xa units, if >90 kg body weight 3750 anti-Xa units) intravenously as a bolus, plus intravenous infusion of 400 anti-Xa units/h for 4 hours, then 300 anti-Xa units/h for 4 hours, then a maintenance infusion of 150-200 anti-Xa units/h for 5-7 days, unless it is required longer in patients for whom there is no reasonable antithrombotic alternative. When it is considered that this intravenous regimen is no longer required, then patients can be converted to oral anticoagulants, or Orgaran 750 anti-Xa units subcutaneously, two or three times a day.
The intended plasma anti-Xa levels are ≤ 1.0 anti-Xa units/mL 5-10 minutes after the bolus, and 0.5-0.8 anti-Xa units/mL during the maintenance infusion.
If the hemofilter life has been seriously shortened by clotting during previous heparin therapy then during the initial hours of the maintenance the infusion rate may have to be higher (up to 600 anti-Xa units/h). This can be continued until the filter life is restored, but the plasma anti-Xa level should not exceed 1.0 anti-Xa units/mL.

Note: continuous renal replacement therapy includes continuous hemofiltration and hemodialysis.
•*Vascular operation or invasive vascular procedure*:
For vascular operations which do not require a by-pass machine, patients ≤90 kg body weight should receivean intravenous bolus of 2250 anti-Xa units before the procedure. For patients >90 kg body weight an intravenous bolus of 3750 anti-Xa units should be administered. No less than 6 hours post-operatively and provided that adequate hemostasis has been achieved, an intravenous infusion of 150-200 anti-Xa units/h for 5-7 days can be given. After several days of intravenous maintenance therapy patients can be converted to oral anticoagulants, or Orgaran 750 anti-Xa units subcutaneously, two or three times a day. The intended plasma anti-Xa levels are 0.5-0.7 anti-Xa units/mL 5-10 minutes after the bolus, and 0.5-0.8 anti-Xa units/mL during the infusion.
Note:
- Vascular operations include: peripheral arterial grafting, endarterectomy, aneurysm repair, and thrombectomy. Invasive vascular procedures include percutaneous transluminal coronary angiography (with and without stenting), insertion/removal of an intra-aortic balloon pump or vena caval filter, cardiac catheterization/angiography, insertion of an arteriovenous shunt etc.
- If angioplasty is carried out during the 6 hours following cardiac catheterization for which this administration regimen has already been instituted, then do not repeat the intravenous bolus.

- No additional intravenous bolus is required to remove a balloon pump in patients who are already receiving Orgaran for thrombosis protection while it is in place.
- *Cardiopulmonary procedures*:

Orgaran has been used for more than 130 cardio-pulmonary operations with by-pass. There is a relatively high frequency of post-operative bleeding, compared with other types of surgery and with medical patients. Orgaran cannot be neutralized by protamine or any other of the usual antagonists to limit bleeding.
Thus, its use is mainly recommended for post-operative prophylaxis in these patients (see below) and should only be used for the surgical procedure in patients for whom no other suitable antithrombotic is available and the operation cannot be postponed until the HIT antibody has been cleared from the circulation (when heparin can be used again just for the surgery) (see section 4.4).
If used for the by-pass procedure then intra-operative, post-thoracotomy, 125 anti-Xa units/kg body weight should be administered intravenously. At the same time, 3 anti-Xa units/mL priming fluid should be added into the pump circuit. At the time of bypass hook-up a 7 anti-Xa units/kg body weight/h intravenous infusion should be started and continued until about 45 minutes prior to expected termination of bypass use. If intra-operative clots are seen then an intravenous bolus of 1250 anti-Xa units (750 anti-Xa units if <55 kg body weight) can be added, but if less than one hour prior to bypass termination extra care must be taken to ensure surgical hemostasis.
If Orgaranor another antithrombotic has been used during cardiopulmonary by-pass surgery and thrombo-prophylaxis is also required post-operatively then Orgarancan be (re)started once adequate hemostasis is achieved (usually 6-12 hours post-operatively) at either 1500-2250 anti-Xa units in divided doses subcutaneously or an intravenous infusion at 150-200 anti-Xa units/h.
Monitoring of plasma anti-Xa levels is generally unnecessary for patient management intra-operatively. If required, then a pre-Orgaransample, a sample 10 minutes after the post-thoracotomy bolus, 10 minutes after the bypass hook-up, two samples during surgery, and one sample in the recovery room should be taken for plasma anti-Xa level monitoring. These will at least help relate the intra- and post-operative bleeding rates to the level of anti-Xa activity at the time. Ideally, using a suitable assay and correct Orgaran reference curve, the plasma anti-Xa activity should be between 1.5 and 2.0 anti-Xa units/mL at its highest and not drop appreciably below 0.8 anti-Xa units/mL during surgery. However, inter-patient responses to the same doses have been variable with peak anti-Xa activity recorded between 0.5 and 2.5 anti-Xa units/mL, which may be due to different assay methods. Nevertheless, intra-patient responses, using the pre-Orgaranlevel as a baseline, are reliable guides to the changes

observed.
Orgaranhas been used successfully in off-pump coronary artery bypass grafting, but the optimal dosing regimen has not been established.

•*Intermittent renal hemodialysis*:
In renal failure, the anticoagulant effects of Orgaran may accumulate causing blood loss. This can be avoided by adjusting the dose according to the pre-dialysis plasma anti-Xa activity of the previous dialysis. After 3-5 dialyses the pre-dialysis dose usually reduces to a steady-state level.
(1) every other day or less frequently: 3750 anti-Xa units (for patients <55 kg body weight 2250 anti-Xa units) intravenously as a bolus just before each of the first two hemodialyses. Prior to each dialysis blood should be drawn for plasma anti-Xa levels, which will be used for determining the Orgarandose for its next dialysis. If plasma anti-Xa levels are <0.3 anti-Xa units/mL then the third or subsequent dialysis dose should be reduced to 3000 units (for patients <55 kg body weight 2000 anti-Xa units). If plasma anti-Xa levels are 0.3-0.35 anti-Xa units/mL then the dose should be reduced to 2250 anti-Xa units (for patients <55 kg body weight use 1500 anti-Xa units). If plasma anti-Xa levels are 0.35-0.4 anti-Xa units/mL then the dose should be reduced to 2000 anti-Xa units (for patients <55 kg body weight 1500 anti-Xa units).

If plasma anti-Xa levels are greater than 0.4 anti-Xa units/mL then Orgaran should not be given prior to dialysis. However, if fibrin threads form in the bubble chamber then the patient may be given 1500 anti-Xa units (irrespective of the patient's weight).
If an Orgaran dose for a dialysis had to be omitted due to a too high pre-dialysis plasma anti-Xa level then the dose for the next dialysis is the same as that used for the dialysis immediately prior to the omitted dose.
During the dialysis the plasma anti-Xa level should be between 0.5-0.8 anti-Xa units/mL.
(2) daily: 3750 anti-Xa units (for patients <55 kg body weight 2250 anti-Xa units) intravenously as a bolus just prior to the first dialysis and 2250 anti-Xa units (for patients <55 kg body weight 2000 anti-Xa units) just prior to the second dialysis. Prior to each dialysis blood should be drawn for plasma anti-Xa levels, which is to be used for dosing the third and subsequent dialyses.

If plasma anti-Xa levels are <0.3 anti-Xa units/mL then the third or subsequent dialysis dose should be reduced to 3000 anti-Xa units (for patients <55 kg body weight 2000 anti-Xa units). If plasma anti-Xa levels are 0.3-0.35 anti-Xa units/mL then the dose should be reduced to 2250 anti-Xa units (for patients <55 kg body weight use 1500 anti-Xa units). If plasma anti-Xa levels are 0.35-0.4 anti-Xa units/mL then the dose should be reduced to 2000 anti-Xa units (for patients <55 kg body weight 1500 anti-Xa units). If plasma anti-Xa levels are greater than 0.4 anti-Xa units/mL then Orgaran should not be given prior to dialysis. However, if fibrin threads subsequently form in the bubble chamber then the patient may be given 1500 anti-Xa units (irrespective of the patient's weight). If an Orgaran dose for a dialysis had to be omitted due to a too high pre-dialysis plasma anti-Xa level then the dose for the next dialysis is the same as that used for the dialysis immediately prior to the omitted dose.
• *Flush doses:* one ampoule of Orgaran is diluted into 50 mL saline. 5-10 mL of this solution can then be used to flush the intravascular lines/access ports as required.
• *Pediatric treatment (age up to 17 years and weight <55 kg)*:
Pediatric experience with Orgaran is limited to 36 children, aged from two weeks to 17 years. The dosing schedules are generalized from the experience so far, however, even children of the same age and weight may respond differently to the dose given. Therefore, dosing should be guided by the plasma anti-Xa response and the balance between desired efficacy and risk of bleeding.

Clinical Situation	Age category	Dosing[1]	Plasma anti-Xa activity
Prophylaxis	≤2 years 7-17 years	8-144 U/kg/day 20-25 U/kg/day	0.1-0.4 U/mL
Treatment	≤2 years 7-17 years	No data bolus i.v. 30 U/kg + 29-130 U/kg/day	0.4-0.7 U/mL post-i.v. bolus 0.4-0.8 U/ML at steady state
Cardiac cathterization	≤2 years 7-17 years	bolus i.v. 18-120 U/kg No data	0.5-0.7 U/mL post-bolus
Hemodialysis	≤2 years 7-17 years	No data Bolus i.v. 27-86 U/kg	0.5-0.8 U/mL intra-dialysis

CAPD[2]	≤2 years 7-17 years	5-43 U/kg/day No data	
Cardiac surgery	≤2 years 7-17 years	350 U/kg/operation >150-311 U/kg/operation	0.8-2.0 U/mL intra-operatively

1: U= anti-Xa unit
2: continuous ambulatory peritoneal dialysis

o*Conversion to oral anticoagulants (vitamin K antagonists) in patients with HIT:*
Conversion to oral anticoagulants (VKAs), is possible both during subcutaneous and intravenous dosing schedules. It is advisable only to start such a therapy when there is adequate antithrombotic control with Orgaran.
(1) Orgaran 750 anti-Xa units subcutaneously two or three times a day: oral anticoagulants (VKAs) can be started 72-96 hours before Orgaran is withdrawn to give time for the prothrombin time, Thrombotest or international normalized ratio (INR) to reach therapeutic levels.
(2) Orgaran 1250 anti-Xa units subcutaneously two or three times a day: when starting oral anticoagulants (VKAs) the Orgaran dose should be reduced to 750 anti-Xa units subcutaneously two or three times a day and the procedure followed as in (1).
(3) Orgaran intravenous infusion: oral anticoagulants (VKAs) can be given with the infusion (maximum rate 300 anti-Xa units/h) which can then be stopped when the INR is in the required target range. If the bleeding risk is high then either (a0 stop the infusion and start Orgaran 750 anti-Xa subcutaneously two or three times a day, then 24 hours later start oral anitcoagulants (VKAs) according to (1), or (b) stop the infusion, give no further Orgaran, then start oral anticoagulants (VKAs) 12 hours later.

<u>b. non-HIT patients (DVT prophylaxis)</u>
In general, Orgaran should be administered by subcutaneous injection at a dose of 750 anti-Xa units for patients ≤90 kg body weight, twice daily for a period of maximally 14 days unless it is required longer in patients for whom there is no reasonable antithrombotic alternative. For patients >90 kg body weight, a dose of 750 anti-Xa untis three times a day or 1250 anti-Xa units twice a day is recommended.
In surgical patients it is recommended to start this dosing schedule pre-operatively and to give the last pre-operative dose 1-4 hours before surgery.

Plasma anti-Xa activity is linearly related to the dose of Orgaran given. In general, monitoring of plasma anti-Xa activity is not necessary. However, in patients suffering from renal insufficiency and/or patients >90 kg body weight monitoring once or twice a week during routine subcutaneous therapy, is recommended to check for drug accumulation or under dosing, respectively. If monitoring of anticoagulant activity is performed then a functional anti-factor Xa test using a specific chromogenic peptide substrate should be used. In this test Orgaran should be used as the standard for constructing the reference curve.

Dosage in the elderly: clearance of anti-factor Xa activity has not been shown to be significantly reduced in the elderly in the absence of moderate to severe renal dysfunction and the usual dosage is recommended.

4.3 Contraindications

1. hepatic jaundice accompanied by a prothrombin time >1.3 times normal
2. hemorrhagic cerebrovascular accident within the previous three months,
3. uncontrollable active bleeding state
4. severe, uncontrolled hypertension
5. diabetic retinopathy
6. acute bacterial endocarditis
7. hypersensitivity to the active substance or to any of the excipients.
8. in patients receiving heparin for treatment rather than for prophylaxis, locoregional anesthesia in elective surgical procedures is contra-indicated.
9. damage to the central nervous system or brain, spinal or ophthalmological surgery.

4.4 Special warnings and precautions for use

Orgaran should not be used if an *in vitro* test for the heparin-induced antibody in the presence of Orgaran is positive in patients with thrombocytopenia induced by heparin or heparin-like anticoagulants, unless no suitable alternative antithrombotic treatment is available.
The incidence of serological cross-reactivity of Orgaran with the heparin-induced antibody before the start of therapy is approximately 5%. The incidence of clinical cross-reactivity developing during Orgaran therapy is approximately 3% and many of these patients had a negative pre-treatment serological cross-reactivity test.
Although the risk of antibody-induced thrombocytopenia and thrombosis during Orgaran therapy (i.e. clinical cross-reactivity) is very small, it is advisable to check the number of platelets daily during the first week of treatment, on alternate days during the second and third weeks, and weekly to monthly thereafter. If a pre-treatment cross-reactivity test with Orgaran is positive but it is decided to use Orgaran, then the number of platelets should be checked daily until Orgaran treatment is stopped.
If antibody-induced thrombocytopenia occurs, one should stop the use of Orgaran and consider alternative treatment.
Orgaran should not be administered to patients with severe hemorrhagic diathesis, e.g. hemophilia and idiopathic thrombocytopenic purpura, unless the patient also has HIT and no suitable alternative antithrombotic treatment is available.
Orgaran should not be used in patients with severe renal and hepatic insufficiency, unless the patient also has HIT and no alternative treatment is available.
Orgaran should not be administered to patients with active gastric or duodenal ulceration, unless it is the reason for operation.
Orgaran should not be given by the intramuscular route.
Orgaran should be used with caution in patients with moderately impaired renal and/or liver function with impaired hemostasis, ulcerative lesions of the gastro-intestinal tract or other diseases which may lead to an increased danger of hemorrhage into a vital organ or site.
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.
Orgaran contains sodium sulfite. In asthma patients hypersensitive to sulfite the latter can result in bronchospasm and/or anaphylactic shock.
It should be noted that the anti-Xa units of Orgaran have a different relationship to clinical efficacy than those of heparin and low molecular weight heparins.
In patients undergoing peridural or spinal anesthesia or spinal puncture, the prophylactic use of heparin may be very rarely associated with epidural or spinal hematoma resulting in prolonged or permanent paralysis. The risk is increased by the use of a peridural or spinal catheter for anesthesia, by the concomitant use of drugs affecting hemostasis such as non-steroidal inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants, and by traumatic or repeated puncture.
In decision-making on the interval between the last administration of a heparin at prophylactic doses and the placement or removal of a peridural or spinal catheter, the product characteristics and the patient profile should be taken into account. Subsequent dose should not take place before at least four hours have elapsed. Re-administration should be delayed until the surgical procedure is completed.
Should a physician decide to administer anticoagulation in the context of peridural or spinal anesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits (numbness and weakness in lower limbs) and bowel or bladder dysfunction. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these.
If signs or symptoms of epidural or spinal hematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Caution remains necessary when administering Orgaran concomitantly with other drugs. However, the evidence from interaction studies in adult healthy volunteers and clinical experience with patients has shown that Orgaran does not appear to interact unfavourably when administered concomitantly with oral anticoagulants (see also section 4.2, Conversion to oral anticoagulants in patients with HIT), drugs which interfere with platelet function and thrombolytics.

Possible interactions with other drugs are difficult to appreciate since most patients receiving Orgaran are also using many various types of drugs, particular for cardiovascular, renal, infectious and respiratory disorders.There is no evidence to date that interaction with these drugs has produced adverse effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
Orgaran has been used in over 60 pregnancies (starting during the first trimester in almost 50% of the pregnancies, the second

trimester in approximately 20% of the pregnancies and the third trimester in 25% of the pregnancies. For a small number of patients the starting trimester is unknown). Overall, the use of Orgaran was successful.
In all five cases in which human umbilical cord blood was tested for the presence of anti-Xa activity, no activity was found.
Caution should be exercised when prescribing to pregnant women. If alternative antithrombotic treatment is unacceptable for medical reasons (e.g. HIT patients) Orgaran can be used.

Lactation
In five cases in which breast milk samples were tested for anti-Xa activity, all showed no or negligible amounts of anti-Xa activity (which would be hydrolyzed in the infant's stomach and rendered harmless).
Although the data are limited, if alternative antithrombotic treatment is unacceptable for medical reasons (e.g. HIT patients) Orgaran can be used during lactation.

4.7 Effects on ability to drive and use machines

Orgaran is not known to have any effect on the ability to drive and use machines.

4.8 Undesirable effects

Orgaranhas the potential to increase the risk of bleeding.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common (≥ 1/100 to 1/10 of patients)	**Uncommon** (≥ 1/1000 to 1/100 of patients)	**Rare** (≥ 1/10000 to 1/1000 of patients)
Blood and the lymphatic system disorders	thrombocytopenia*, heparin-induced thrombocytopenia		auto-immune thrombocytopenia
Immune system disorders		hypersensitivity, drug hypersensitivity	
Skin and subcutaneous tissue disorders	rash	purpura, rash maculo-papular, rash erythematous, pruritus, urticaria	rash generalised, rash maculovesicular, injection or infusion site rash, rash macular
General disorders and administration site conditions		injection site reaction	Injection (inj) site: -haemorrhage -discomfort -hypersensitivity -irritation -coldness -pruritus inj. or infusion site: -erythema -pain -swelling -warmth infusion site: -bruising -reaction
Injury, poisoning and procedural complications	post procedural haemorrhage	post procedural haematoma, operative haemorrhage	incision site haemorrhage, anastomotic haemorrhage

Antibody-induced thrombocytopenia, as can be caused by (low molecular weight) heparin, was observed in rare cases during the use of Orgaran, but only in patients who were already sensitized to either heparin or low molecular weight heparin (see Section 4.4).
Note: terms are coded with MedDRA dictionary version 8.1
All above terms in this section and synonym terms (with same or less severity) coded with the MedDRA dictionary are considered as 'listed'.
All hemorrhages are listed adverse events for Orgaran.This also means that symptoms or signs which are clearly directly related to a hemorrhage (e.g. anemia, decreased Hb, rbc, hematocrit, faintness, tiredness, tamponade) are listed adverse events.
Very rarely, cases of epidural and spinal hematomas were reported in association with prophylactic use of heparin in the context of peridural or spinal anesthesia and of spinal puncture.
These hematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see section 4.4).

4.9 Overdose

In the event of serious bleeding other than caused by a surgical error, Orgaran should be stopped and transfusion of fresh frozen plasma or, if controllable, plasmapheresis should be considered.Although protamine partially neutralises the anticoagulant activity of Orgaran the relevance for the reversal of the bleeding is not clear and therefore cannot be recommended. The effects of Orgaran on anti-Xa activity cannot be antagonized with any known agent at this time.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, heparin group;
ATC code B01A B09

Danaparoid sodium has been shown both in animal models and in human studies to be an effective antithrombotic substance. At therapeutic doses danaparoid sodium has no or only a minor effect on hemostatic plug formation, platelet function and platelet aggregability with no significant effect on bleeding time at the recommended doses. Occasionally, after high intravenous or subcutaneous doses, a prolonged bleeding time has been observed. The anticoagulant activity of danaparoid sodium in clotting assays such as prothrombin time, activated partial thromboplastin time, kaolin cephalin clotting time and thrombin time is small, and characterised by a very flat dose-response curve up to relatively high doses.
The ultimate step in blood coagulation, the fibrinogen-fibrin conversion, is critically dependent on thrombin generation to which factor Xa and thrombin contribute substantially. The anticoagulant profile of danaparoid sodium is characterised by a high ratio of anti-factor Xa/antithrombin activities, resulting in an effective inhibition of thrombin generation and thrombus formation. The anti-Xa activity is mediated by antithrombin and is not inactivated by endogenous heparin- neutralising factors. The small thrombin inhibitory activity is mediated by heparin co-factor II and antithrombin. The heparan sulfate fraction with low affinity for antithrombin, lacking significant effects on coagulation factors Xa and IIa *in vitro*, has been shown in animal studies to contribute substantially to the antithrombotic activity which is only in part explained by an inhibitory effect on thrombin mediated activation of clotting factor IX.
Orgaran shows low serological cross-reactivity (5%) with the heparin-induced antibody. This can be explained by the absence of heparin in Orgaran and its low degree of both sulfation and negative charge (see section 4.4 "Special warnings and precautions for use").

5.2 Pharmacokinetic properties

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 thrombin generation inhibitory activity and antithrombotic activities of danaparoid sodium were strongly related but the simplest to measure is the effect on plasma anti-Xa activity. The absolute bioavailability of danaparoid sodium, as estimated from its effect on plasma anti-Xa activity, after subcutaneous administration approaches 100%. In humans 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 of approximately 25 hours and 7 hours respectively, after both subcutaneous and intravenous administration are independent of dose, age and gender. 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 is prolonged.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of reproductive and developmental toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium sulfite, anhydrous (E221)
Sodium chloride
Hydrochloric acid (to adjust the pH)
Water for injections

6.2 Incompatibilities

When administered as an intravenous bolus or infusion, Orgaran should be given separately and not be mixed with other drugs. However, Organon is compatible with and can be added to the infusions mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years
Once opened: Chemical and physical in-use stability of Orgaran diluted in common infusion fluids has been demonstrated for up to 48 hours below 25˚C. Do not refrigerate or freeze.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions of the diluted solution, see section 6.3.

Do not freeze. Keep the ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

Box with ten or twenty 1-ml type I glass ampoules containing 750 anti-factor Xa units (0.6ml) danaproid sodium per ampoule (1250 anti-factor Xa units/ml).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Orgaran is compatible with, and therefore can be added to, infusions of saline (0.9%), dextrose (5%), dextrose-saline, Ringer's and lactated Ringer's. Discard the product when the visual appearance has changed or when the container is damaged.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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