ORGANAR

(i) NAME OF THE MEDICINAL PRODUCT

Orgaran®

(ii) DESCRIPTION

Orgaran is supplied in ampoules each containing 750 anti-Xa units (approx. 55 mg) danaparoid sodium, as a sterile, isotonic solution of pH 7 in 0.6mL Water for Injections suitable for subcutaneous injection.

Composition

Orgaran contains danaparoid sodium, which is a mixture of low molecular weight sulfated glycosaminoglycuronans derived from animal mucosa, comprising heparan sulfate, dermatan sulfate and a minor amount of chondroitin sulfate. One mL contains 1250 amidolytic anti-Factor Xa units (approx. 90 mg) danaparoid sodium and 0.15% (w/v) sodium sulfite. The anti-Xa unit is derived from the international heparin standard in an antithrombin-III containing buffer system.

(iii) PHARMACOLOGY

Pharmacology

Danaparoid sodium has been shown both in animal models and in human studies to be an effective antithrombotic substance. Danaparoid sodium has a negligible effect on haemostatic plug formation, platelet function and platelet aggregability. In animal models it produces less bleeding enhancing activity than heparin whilst in human studies the effects of Orgaran and heparin were found to be similar.

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 (approx. 20/1), resulting in an effective inhibition of thrombin generation and thrombus formation with minimal bleeding enhancing activity. The anti-Xa activity is mediated by antithrombin-III and is not inactivated by endogenous heparin-neutralising factors. The small antithrombin activity is mediated by heparin co-factor II and antithrombin-III. The heparan sulfate fraction with low affinity for antithrombin-III, lacking significant effects on coagulation Factors Xa and IIa in vitro, has been shown in animal studies to contribute substantially (approx. 50%) to the antithrombotic activity by an as yet unexplained mechanism. The risk of haemorrhage with this drug is not related with plasma anti-Xa activity, within the therapeutic dose range.

Pharmacokinetics

Pharmacokinetic studies were primarily based on the kinetics of relevant anticoagulant activities of danaparoid sodium, as no specific chemical assay methods are available. The absolute bioavailability of danaparoid sodium 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 the dose and route of administration. Although plasma clearance of anti-Xa activity
was found to be 20% lower in female volunteers than in male volunteers, this difference is not significant. 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. 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 (see Dosage and Administration).

Clinical studies have demonstrated that the clinical activity of danaparoid sodium may not relate to the dose expressed as either milligrams or anti-Xa activity.

(iv) INDICATIONS

Orgaran is indicated for the prevention of postoperative venous thromboembolism in patients undergoing general or orthopaedic surgery.

(v) CONTRAINDICATIONS

- severe haemorrhagic diathesis e.g. haemophilia and idiopathic thrombo-cytopenic purpura
- haemorrhagic stroke in the acute phase
- uncontrollable active bleeding state
- hypersensitivity to Orgaran
- hypersensitivity to sulfite
- a positive in vitro aggregation test in the presence of Orgaran in patients with a history of thrombocytopenia induced by heparin-like anticoagulants
- severe renal and/or hepatic insufficiency
- severe hypertension
- severe gastric or duodenal ulcer, unless it is the reason for operating
- acute bacterial endocarditis
- diabetic retinopathy

(vi) PRECAUTIONS

Orgaran and Low Molecular Weight Heparins are not interchangeable clinically.

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 haemostasis, ulcerative lesions of the gastro-intestinal tract or other diseases/conditions which may lead to an increased danger of haemorrhage into a vital organ or site.

Orgaran contains sodium sulfite. In asthmatic patients hypersensitive to sulfite the latter can result in bronchospasm and/or anaphylactic shock.

Orgaran has very little cross-reactivity in producing thrombocytopenia in patients with a previous history of heparin-induced thrombocytopenia syndrome (HITS). Cross-reactivity in vitro between danaparoid sodium and heparin in producing immune platelet aggregation occurred in only 9% of patients tested. Orgaran can be administered to patients sensitised by heparin after cross-reactivity with Orgaran has been ruled out by an in vitro test.

The anticoagulant activity of Orgaran is characterised 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.

No incidences of osteoporosis have been reported in patients treated with the recommended dose of Orgaran. However, as for heparin, treatment with a glycosaminoglycoronan may result in osteoporosis if the dosage is inappropriate.
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.

**Spinal/Epidural haematomas**

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

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

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

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

**Use in pregnancy (Category C)**

In rats, doses of danaparoid greater than 100 anti-Xa units/kg/day administered IV during gestation reduced postnatal weight gain of the offspring. Higher doses, up to 1600 anti-Xa units/kg/day, did not cause any other matermotoxic or teratogenic effects. In rabbits, IV doses up to 800 anti-Xa units/kg/day did not cause any foetal malformations, but the highest dose used was insufficient to rule out the possibility of teratogenic activity in this species. The use of Orgaran in human pregnancy has only been studied incidentally. Observations in pregnant women have so far given no indication that the use of Orgaran during pregnancy leads to foetal abnormalities or to exacerbation of bleeding in mother or infant during delivery.

**Use in lactation**

There is no data available on Orgaran secretion into breast milk.

**Carcinogenesis and Mutagenesis**

Long-term animal carcinogenicity studies of Orgaran have not been done. A standard battery of mutagenicity tests has not shown any evidence of genotoxic potential.

**Interactions with other drugs**

In clinical studies no clinically significant interactions with other medications have been found.

Orgaran may be used together with oral anticoagulants or drugs which interfere with platelet function, such as aspirin and non-steroidal anti-inflammatory drugs, or potentially ulcerogenic drugs (such as corticosteroids), but caution remains necessary. Combination of Orgaran with aspirin may cause a prolongation of the bleeding time.

Monitoring of anticoagulant activity of oral anticoagulants by prothrombin time and Thrombotest is unreliable within 5 hours following Orgaran administration.

**(vii) ADVERSE REACTIONS**

Bruising and/or pain may occur at injection sites. Skin rashes and other local or generalised hypersensitivity reactions have occasionally been observed (see Table).
<table>
<thead>
<tr>
<th></th>
<th>Orgaran</th>
<th>Heparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction at injection site incl. pain</td>
<td>15%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain (general)</td>
<td>1.6%</td>
<td>1.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>0.3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased bleeding</td>
<td>45%</td>
<td>69%</td>
<td>23%</td>
</tr>
</tbody>
</table>

As with heparin, Orgaran may induce thrombocytopenia, although to date this has not been observed. The platelet count should therefore be monitored at regular intervals.

Liver abnormalities such as changes in transaminase and alkaline phosphates have been observed, but no clinical significance has been demonstrated.

**(viii) DOSAGE AND ADMINISTRATION**

Orgaran is administered by subcutaneous injection at a dose of 750 anti-Factor Xa units, twice daily for 7 to 10 days. In human studies, its safety has only been demonstrated for the use of up to 10 postoperative days duration.

In surgical patients it is recommended to give the last pre-operative dose 1-4 hours before surgery.

**Dosage in the elderly:** Clearance of anti-Factor Xa activity has not been shown to be markedly reduced in the elderly and the usual dosage is recommended.

Plasma anti-Xa activity is linearly related to the dose of Orgaran given. The steady state plasma anti-Xa response is 0.15-0.35 units per mL following the recommended subcutaneous dose of Orgaran. If it is necessary to monitor anticoagulant activity, and for individual dose setting, a functional anti-Factor Xa test using a chromogenic peptide substrate should be used. In this test Orgaran should be used as the standard.

**(ix) OVERDOSAGE**

In the event of serious bleeding other than caused by a surgical error, Orgaran should be stopped and blood transfusion considered. Although protamine partially neutralises the anticoagulant activity of Orgaran, it is likely to be of little use in reversing the potential bleeding complications associated with overdosage and therefore cannot be recommended.

**(x) PRESENTATION**

Pack of ten ampoules each containing 750 anti-Xa units danaparoid sodium in 0.6 mL Water for Injections.
(xi) STORAGE CONDITIONS

Three years shelf life when stored below 30°C.
Protect from light.

Aust R No. 46096

Distributed by:
Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street,
South Granville, NSW 2142
Australia

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Date of latest safety notification: 25/05/05
Date of most recent amendment: 2 September 2011

The information supplied relates only to ORGARAN and should not be used in relation to any other product which may also contain the same active ingredients.