SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Danaparoid sodium 750 anti-Xa units/0.6 ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 0.6 mL contains 750 amidolytic anti-factor Xa units danaparoid sodium (1250 anti-factor Xa units per mL).

The anti-Xa unit is derived from the international heparin standard in an antithrombin containing buffer system.

Danaparoid sodium is produced from porcine intestinal mucosa

Excipient with known effect:

Each 0.6 mL ampoule contains up to 0.9 mg sodium sulfite

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is a clear, colourless to light yellow liquid

pH 6.0-7.5

Osmolality 300 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

· Prevention of deep vein thrombosis and its possible consequences in patients undergoing general or orthopaedic surgery.

· Treatment of thrombo-embolic disorders in patients who require urgent parenteral anti-coagulation because of the development or history of heparin-induced thrombocytopenia (HIT).

4.2 Posology and method of administration

Posology

a) Non-HIT patients (DVT prophylaxis)

In general, Danaparoid sodium should be administered by subcutaneous injection at a dose of 750 anti-factor Xa units, twice daily for 7 to 10 days or until the risk of thromboembolism has diminished.

In surgical patients it is recommended to start this dosing 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 Danaparoid Sodium given. 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 Danaparoid Sodium should be used as standard for constructing the reference curve.

b) HIT patients

The diagnosis of HIT should as a minimum be based on:

1) thrombocytopenia (platelet count<$100x10^9$/L) occurring during heparin administration and
2) exclusion of all other causes of thrombocytopenia

In general monitoring of plasma anti-Xa activity is not necessary. However, in patients suffering from renal insufficiency and/or patients weighing over 90kg, monitoring (using an amidolytic assay) is recommended.

Danaparoid Sodium should be administered intravenously as a bolus of 2500 anti-Xa units (for patients less than 55kg 1250 units, if over 90kg, 3750 units) followed by an intravenous infusion of 400units/h for 2 hours, then 300 units/h for 2 hours, then a maintenance infusion of 200 units/h for 5 days. The expected plasma anti-Xa levels are 0.5-0.7 units/ml 5-10 minutes after the bolus, not higher than 1.0 units/ml during the adjustment phase of maintenance infusion and 0.5-0.8 units/ml during the maintenance infusion.

Elderly:

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

Children (age up to 17 years):

There is insufficient experience with the use of Danaparoid Sodium in children to suggest a dosage regimen for this group of patients.

Hepatic or renal impairment:
Danaparoid Sodium should be used with caution in patients with moderately impaired renal and/or liver function with impaired haemostasis.

Conversion to anticoagulants is possible, however it is advisable only to start such a therapy once there is adequate antithrombotic control with Danaparoid Sodium.
Oral anticoagulants can be given with the infusion (maximum rate 300units/h) which can then be stopped when the international normalised ratio is ≥1.5. If the bleeding risk is high then either:
(a) stop the infusion and start Danaparoid Sodium 750 anti-Xa units/0.6 ml subcutaneously twice a day, then 24 hours later start anticoagulants 48-72 hours before Danaparoid Sodium is withdrawn to give time for the prothrombin time, Thrombotest and international normalised ratio to reach therapeutic levels (measurement of these parameters is not reliable within 5 hours of Danaparoid Sodium injection (See "Interactions with other medicaments and other forms of interactions")) or
(b) stop the infusion, give no further Danaparoid Sodium then start the anticoagulants 12 hours later.

Method of administration
For subcutaneous or intravenous use
Solutions may be diluted before use. See section 6.6.

4.3 Contraindications

As with heparins, in patients receiving Danaparoid Sodium for treatment rather than for prophylaxis, locoregional anaesthesia in elective surgical procedures is contra-indicated.

* severe haemorrhagic diathesis, e.g. haemophilia and idiopathic thrombocytopenic purpura, unless the patient also has HIT and no alternative anti-thrombotic treatment is available
* haemorrhagic stroke in the acute phase
* uncontrollable active bleeding state
* severe renal- and/or hepatic insufficiency, unless the patient also has HIT and no alternative anti-thrombotic treatment is available
* severe uncontrolled hypertension
* active gastroduodenal ulcer, unless it is the reason for operation
* diabetic retinopathy
* acute bacterial endocarditis

* a positive in vitro aggregation test for the heparin-induced antibody in the presence of Danaparoid Sodium in patients with a history of thrombocytopenia induced by heparin or heparin-like anticoagulants
* hypersensitivity to sulfite.
* hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Danaparoid Sodium should not be used if an in vitro test for the heparin-induced antibody in the presence of Danaparoid Sodium 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 Danaparoid Sodium with the heparin-induced antibody before the start of therapy is approximately 5%. The incidence of clinical cross-reactivity developing during Danaparoid Sodium 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 Danaparoid Sodium 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 Danaparoid Sodium is positive but it is decided to use Danaparoid Sodium, then the number of platelets should be checked daily until Danaparoid Sodium treatment is stopped. If antibody-induced thrombocytopenia occurs, one should stop the use of Danaparoid Sodium and consider alternative treatment.

Danaparoid Sodium should not be administered to patients with severe haemorrhagic diathesis, e.g. haemophilia and idiopathic thrombocytopenic purpura, unless the patient also has HIT and no suitable alternative antithrombotic treatment is available.

Danaparoid Sodium should not be used in patients with severe renal and hepatic insufficiency unless the patient also has HIT and no alternative antithrombotic treatment is available.

Danaparoid Sodium 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 which may lead to an increased danger of haemorrhage into a vital organ or site.

Danaparoid Sodium should not be administered to patients with active gastric or duodenal ulceration, unless it is the reason for operation.

- Since severe bleeding may occur post-operatively in HIT patients undergoing a cardiopulmonary bypass procedure, Danaparoid Sodium is not recommended during the procedure, unless no other antithrombotic treatment is available.
- Danaparoid Sodium should not be given by the intramuscular route.
- The safety and efficacy of Danaparoid Sodium in patients with non-haemorrhagic stroke remains to be confirmed.
- No incidences of osteoporosis have been reported in patients treated with the recommended dose of Danaparoid Sodium. However, as for heparin, treatment with glycosaminoglycuronan may result in osteoporosis if the dosage is inappropriate.
- It should be noted that the anti-Xa units of Danaparoid Sodium have a different relationship to clinical efficacy than those of heparin and low molecular weight heparins.
- As with heparins, in patients undergoing peridural or spinal anaesthesia or spinal puncture, the prophylactic use of Danaparoid Sodium may theoretically be associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. The risk is increased by the prolonged use of a peridural or spinal catheter for analgesia, by the concomitant use of drugs affecting haemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), and by traumatic or repeated puncture.
- In decision-making on the interval between the last administration of Danaparoid Sodium 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 Danaparoid Sodium in the context of peridural or spinal anaesthesia, 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 haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

This medicinal product contains sodium sulfite. May rarely cause severe hypersensitivity reactions and bronchospasm.
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies no clinically significant interactions with other medications have been found. Danaparoid Sodium may be used together with oral anticoagulants, 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 this is particularly important in patients undergoing peridural or spinal anaesthesia or spinal puncture (see section 4.4.). Monitoring of anticoagulant activity of oral anticoagulants by prothrombin time and thrombotest is unreliable within 5 hours after Danaparoid Sodium administration.
There is no data available on the effect of Danaparoid Sodium on thyroid function tests

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Danaparoid Sodium 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 Danaparoid Sodium was successful.

Animal studies have not demonstrated any teratogenic effect or placental transfer. In the few cases in which human umbilical cord blood was tested for the presence of anti-Xa activity, no activity was found.

Although Danaparoid Sodium has been used with success in a small number of pregnancies, the available information is still considered to be insufficient to assess whether deleterious effects may occur in pregnancy during the use of Danaparoid Sodium.

Caution should be exercised when prescribing to pregnant women. If alternative antithrombotic treatment is unacceptable for medical reasons (e.g. HIT patients) Danaparoid Sodium can be used.

Breast-feeding

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) Danaparoid Sodium can be used during lactation.

Fertility

There are no clinical studies on the effect of danaparoid sodium on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Enhanced bleeding or haematoma may occur at the operation site.
Bruising and/or pain may occur at injection sites.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	**Common (≥1/100 to 1/10 of patients)**	**Uncommon (≥1/1,000 to 1/100 of patients)**	**Rare (≥1/10,000 to <1/1,000 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 hematoma, operative haemorrhage	incision site haemorrhage, anastomotic haemorrhage

Note: terms are coded with MedDRA dictionary

Antibody induced thrombocytopenia, as can be caused by (low molecular weight) heparin, was observed in rare cases during the use of Danaparoid Sodium, but only in patients who were already sensitised to either heparin or low molecular weight heparin (see section 4.4).

All above terms in this section and synonym terms (with same or less severity) coded with the MedDRA dictionary are considered as 'listed'.

All haemorrhages are listed adverse events for Danaparoid Sodium. This also means that symptoms or signs which are clearly directly related to a haemorrhage (e.g. anaemia, decreased Hb, rbc, hematocrit, faintness, tiredness, tamponade) are listed adverse events.

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

Very rarely, cases of epidural and spinal haematomas were reported in association with prophylactic use of heparins in the context of peridural or spinal anaesthesia and of spinal puncture. These haematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see Section 4.4 'Special warnings and precautions for use').

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of serious bleeding other than caused by a surgical error, Danaparoid Sodium should be stopped and transfusion of fresh frozen plasma or, if uncontrollable, plasmapheresis should be considered. Although protamine partially neutralises the anticoagulant activity of Danaparoid Sodium the relevance for the reversal of the bleeding is not clear and therefore cannot be recommended. The effects of Danaparoid Sodium 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 is a non-heparin mixture of low molecular weight sulphated glycosaminoglycuronans derived from animal mucosa, comprising heparan sulphate, dermatan sulphate and a minor amount of chondroitin sulphates.

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 haemostatic 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 prothrombin 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 prothrombin 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-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 sulphate 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 to the antithrombotic activity by an as yet unexplained mechanism.

Danaparoid Sodium shows low cross-reactivity (<10%) with the heparin induced antibody. This can be explained by the absence of heparin in Danaparoid Sodium and its low degree of sulphation (see section 4.4).

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.

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. 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.

5.3 Preclinical safety data

The results of pre-clinical studies do not add to the information included in the other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium sulfite
Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

When administered as an intravenous bolus or infusion, Danaparoid Sodium should be given separately and not mixed with other drugs. However, Danaparoid Sodium is compatible with, and therefore can be added to, infusions of saline, dextrose or dextrose-saline.

6.3 Shelf life

Ampoules unopened: 3 years.

Diluted solutions
Chemical and physical in-use stability has been demonstrated for 48 hours at 25ºC (room temperature).

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 and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

1-ml type 1 colourless glass ampoules containing 750 anti-factor Xa units (0.6ml) danaparoid sodium per ampoule (1250 anti-factor Xa units/ml) in packs of 10 or 20 ampoules.

6.6 Special precautions for disposal

Solutions may be diluted with infusions of saline, dextrose or dextrose-saline.
Any unused medicinal product or waste material should be disposed of in accordance
with local requirements.

7 MARKETING AUTHORISATION HOLDER

Generics UK Limited t/a Mylan

Station close, Potters Bar

Hertfordshire

EN6 ITL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1859

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