DATA SHEET
Innohep® (Tinzaparin sodium: Low Molecular Weight Heparin)
10,000 anti Xa IU/mL
20,000 anti Xa IU/mL

PRESENTATION
Innohep® contains tinzaparin sodium (low molecular weight heparin of porcine origin) in a sterile solution for subcutaneous injection, presented in unit-dose prefilled syringes, and multi-dose vials.

Innohep® unit dose syringes contain:
- tinzaparin sodium 10,000 anti-Xa IU/mL in 0.45mL without preservative
- tinzaparin sodium 20,000 anti-Xa IU/mL in 0.5mL with sodium metabisulfite
- tinzaparin sodium 20,000 anti-Xa IU/mL in 0.7mL with sodium metabisulfite
- tinzaparin sodium 20,000 anti-Xa IU/mL in 0.9mL with sodium metabisulfite

Innohep® 2mL vials contain 20,000 anti-Xa IU/mL with sodium metabisulfite, benzyl alcohol and water for injections (see also PACKAGING QUANTITIES at the end of this document).

Not all presentations may be available.

USES

ACTIONS
Innohep® is an antithrombotic agent. It potentiates the inhibition of several activated coagulation factors, especially Factor Xa, its activity being mediated via Antithrombin III.

PHARMACOKINETICS
The pharmacokinetics/pharmacodynamics of Innohep® are monitored by anti-Xa activity. Innohep® has a bioavailability of around 90% following subcutaneous injection. The absorption half-life is 200 minutes, peak plasma activity being observed after 4-6 hours. The elimination half-life is about 90 minutes. There is a linear dose response relationship between plasma activity and the dose administered.

The pharmacokinetic activities of Innohep® have been studied in pregnancy. Data from sequential pharmacokinetic monitoring in 55 pregnancies suggests that pharmacokinetic properties do not differ from the non-pregnant state. There was a small, but non-statistically significant, decrease in anti-Xa levels with advancing gestation.

INDICATIONS
For prevention of thromboembolic events including deep vein thrombosis, in patients undergoing general and orthopaedic surgery, treatment of deep vein thrombosis, treatment of pulmonary embolism and prevention of coagulation of blood in extra-corporeal circulation, such as haemodialysis.

DOSAGE AND ADMINISTRATION

Treatment of Deep Vein Thrombosis:-
175 anti-Xa IU/kg body weight by subcutaneous injection once daily.

Prophylaxis of Deep Vein Thrombosis:-
General surgery, 3500 anti-Xa IU by subcutaneous injection 2 hours preoperatively, then once a day for 7 to 10 days.
Orthopaedic surgery, 50 anti-Xa IU/kg body weight subcutaneously 2 hours preoperatively, followed by a once - daily dose, Or 4500 IU subcutaneously 12 hours preoperatively, followed by a once - daily dose, until the patient has been mobilised.
Haemodialysis, for periods less than 4 hours, a bolus dose of 2000 to 2500 anti-Xa IU into the arterial side of the dialyser (or intravenously), at the beginning of dialysis. For periods of more than 4 hours, a bolus dose of 2500 anti-Xa IU into the arterial side of the dialyser (or intravenously) at the beginning of the dialysis, followed by an infusion of 750 anti-Xa IU/hour. The dialyser can be primed by flushing with 500 - 1000mL isotonic sodium chloride (9mg/mL) containing 5000 anti-Factor Xa IU Innohep® per litre.

**Treatment of pulmonary embolism:-**
Single daily subcutaneous injection of 175 anti-Xa IU/kg.

**Liver and Kidney Insufficiency:-**
Innohep® therapy should be given with caution to patients with severe liver or kidney insufficiency. In such cases a dose reduction should be considered.

**Renal impairment:-**
No dose reduction is needed in patients having creatinine clearance levels down to 20 ml/min. However, precaution is recommended when treating patients with severe renal impairment (creatinine clearance < 30 ml/min) (see WARNINGS AND PRECAUTIONS section).

**Children:-**
There is no experience of use in children.

**Elderly:-**
No dose reduction is needed in elderly patients with normal renal function. Elderly patients with severe renal impairment (creatinine clearance < 30ml/min) should be monitored (see WARNINGS AND PRECAUTIONS section).
Renal function should be assessed (using for example the Cockcroft-Gault formula) to estimate creatinine clearance levels.

**CONTRAINDICATIONS**
Innohep® is contraindicated in patients with:
- known hypersensitivity to fractionated or unfractionated heparins, or any of the excipients of Innohep® as listed under ‘PRESENTATION’;
- a current history of immune-mediated heparin-associated thrombocytopenia (type II);
- septic endocarditis

The use of Innohep® is contraindicated for patients with active major haemorrhage or conditions predisposing to major haemorrhage. Major haemorrhage is defined as haemorrhage which fulfils any one of these three criteria: a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intrauterine or intramuscular with compartment syndrome), b) causes a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or c) leads to transfusion of two or more units of whole blood or red blood cells.

Treatment doses (but not prophylactic doses) of Innohep® are contraindicated in patients who receive neuraxial anaesthesia (e.g. spinal or epidural anaesthesia, or lumbar puncture). Use of Innohep® should be discontinued at least 24 hours before the procedure is performed. Innohep should not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after the catheter has been removed. Patients should be closely monitored for signs and symptoms of neurological injury. See ‘WARNINGS AND PRECAUTIONS’ for further information on prophylactic doses and use in pregnancy.

The multidose vial formulations of Innohep® contain 10 mg/mL of the preservative benzyl alcohol. These formulations must not be given to premature babies and neonates due to the risk of gasping syndrome.

**WARNINGS AND PRECAUTIONS**
Innohep® should not be administered:
- by intramuscular injection due to the risk of haematoma. Concomitant intramuscular injections of other medicines should also be avoided;
- by intravenous injection;
- in patients with uncontrolled arterial hypertension;
• in suspected malignancy with bleeding tendency;
• in patients with nephrolith or ureterolith;
• concomitantly with drugs which increase the serum potassium level, or with platelet inhibitors (eg. aspirin, ASA);
• in patients with asthma and hypersensitivity to sulfites, as Innohep® contains sodium bisulfite.

Innohep® therapy should be given with caution:
• to patients with severe liver or kidney insufficiency. In such cases a dose reduction should be considered;
• to patients on oral anti-coagulants;
• in the treatment of elderly patients;
• to patients at risk of haemorrhage (for patients at risk of major haemorrhage see ‘CONTRAINDICATIONS’)

Caution is advised when performing neuraxial anaesthesia or lumbar puncture in patients receiving prophylactic doses of Innohep® due to the risk of spinal haematomas resulting in prolonged or permanent paralysis. A minimum delay of 12 hours should be allowed between the last prophylactic dose and the needle or catheter placement. For continuous techniques, a similar delay should be observed before removing the catheter. Treatment with Innohep® should not be resumed until at least 4-6 hours after spinal anaesthesia or after the catheter has been removed. Patients should be closely monitored for signs and symptoms of neurological injury.

Platelet counts are recommended: before administration of Innohep®, on the first day of therapy and then regularly every 3 or 4 days, and at the end of therapy. Innohep® should be discontinued in patients who develop immune-mediated heparin-induced thrombocytopenia (type II). Platelet counts will usually normalise within 2 to 4 weeks after withdrawal.

Heparin products can suppress adrenal secretion of aldosterone, leading to hyperkalaemia. Risk factors include diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium at pre-treatment, concomitant therapy with drugs that may elevate plasma potassium, and long-term use of Innohep®. In patients at risk, potassium levels should be measured before starting Innohep® and monitored regularly thereafter. Heparin-related hyperkalaemia is usually reversible upon treatment discontinuation, though other approaches may need to be considered (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance) if Innohep® treatment is considered lifesaving.

Precaution is recommended in the treatment of patients with severe renal impairment (creatinine clearance < 30 mL/min). Available evidence demonstrates no accumulation in patients with creatinine clearance levels down to 20 ml/minute. Although anti-Xa monitoring is the most appropriate measure of the pharmacodynamic effects of Innohep®, it remains a poor predictor of haemorrhage risk, nonetheless monitoring of anti-factor Xa activity may be considered in patients with severe renal impairment (creatinine clearance<30 ml/min). There is limited data available in patients with an estimated creatinine clearance level below 20 ml/minute.

Precaution is recommended in the treatment of elderly patients as they are more likely to have reduced renal function.

The multidose vial formulations of Innohep® contain 10 mg/mL of the preservative benzyl alcohol. Benzyl alcohol may cause toxic and allergic reactions in infants and children up to three years of age.

There is no experience with the use of Innohep® in the treatment of children.

Regarding the ability of those receiving treatment to drive or use machinery, Innohep® is considered safe or unlikely to produce an effect.

**Pregnancy and Lactation**

Pregnancy: Category B1

Data from pregnant women (more than 2,200 pregnancy outcomes) indicate no foetal/ neonatal toxicity or malformation due to tinzaparin. Tinzaparin does not cross the placenta. Tinzaparin can be used during all trimesters of pregnancy if clinically needed. Caution should be exercised when prescribing tinzaparin to pregnant women.
Animal data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Due to the risk of spinal haematoma, treatment doses of Innohep® (175 anti-Xa IU/kg) are contraindicated in patients who receive neuraxial anaesthesia. Therefore, epidural anaesthesia in pregnant women should always be delayed until at least 24 hours after administration of the last treatment dose of Innohep® and the needle or catheter placement. See ‘CONTRAINDICATIONS’ section of this datasheet for more information.

Pregnant patients with prosthetic heart valves
Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anticoagulant doses of tinzaparin and other LMWHs. Tinzaparin is not recommended for use in pregnant women with prosthetic heart valves. In the absence of clear dosing, efficacy and safety information in this circumstance, any attempt to anti-coagulate such patients must only be undertaken by medical practitioners with expertise and experience in this clinical area, and only if no safer alternative is available.

Cases of “Gasping Syndrome” have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-404 mg/kg/day). See ‘CONTRAINDICATIONS’ section. The 2 mL vial of Innohep® 20,000 IU/mL contains 20 mg of benzyl alcohol (10 mg of benzyl alcohol per mL). As benzyl alcohol may cross the placenta, the use of Innohep® formulations containing benzyl alcohol is not recommended during pregnancy.

Animal data indicate that Innohep® excretion into breast milk is minimal. It is not known whether tinzaparin is excreted into human breast milk. Although oral absorption of low molecular weight heparins is unlikely, a risk to the newborn infants cannot be excluded. In certain women, the incidence of venous thromboembolism is particularly high during the first six weeks after child birth. A decision must be made whether to stop breast-feeding or discontinue Innohep® therapy taking into account the benefit of breast-feeding for the child and the benefit of Innohep® therapy for the mother.

There are no clinical studies regarding the effect of Innohep® on fertility.

**ADVERSE EFFECTS**

Haemorrhage events are one of the most frequently reported adverse events when using Innohep®. Haemorrhage may present in any organ and have different degrees of severity. Complications may occur particularly when high doses of Innohep® are administered. Although major haemorrhages are uncommon, death or permanent disability has been reported in some cases.

Immune-related heparin-induced thrombocytopenia (type II) largely manifests within 5 to 14 days of receiving the first dose. Furthermore, a rapid-onset form has been described in patients previously exposed to heparin. Innohep® must be discontinued in all cases of immune-related heparin-induced thrombocytopenia. Immune-mediated heparin-induced thrombocytopenia (type II) may be associated with arterial and venous thrombosis.

The estimation of the frequency of adverse effects is based on a pooled analysis of data from clinical studies and from spontaneous reporting.

**Frequent: ≥1/100 and <1/10 (≥1% and <10%)**
- haemorrhage or haematoma
- anaemia (including decreased haemoglobin);
- increase in serum potassium concentration;
- increase in gamma-glutamyltransf erase (GGT), lactodehydrogenase (LDH), lipase;
- injection site reaction including haematoma, haemorrhage, nodule, erythema, extravasation and pain;
- as for conventional heparin, a transient increase in aminotransferase levels is frequently observed.
  Cessation of treatment is not usually required.

**Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)**
- thrombocytopenia (type I) (including decrease in platelet count)
- hypersensitivity
- bruising, ecchymosis and purpura
- hepatic enzymes increased (including increased transaminases, ALT, AST and GGT)
- dermatitis, rash and/or purititis
Rare: $\geq 1/10,000$ and $<1/1000$ ($\geq 0.01\%$ and $<0.1\%)$

- cases of severe immune-mediated thrombocytopenia (type II), with platelet counts below $100 \times 10^9$/$L$ or a rapid decrease to 50% of baseline platelet count, have been observed;
- thrombocytosis;
- anaphylactoid reactions; anaphylactic shock, allergic reactions with symptoms such as nausea, vomiting, fever, headache, urticaria, pruritus, dyspnoea, bronchospasm, hypotension;
- transient scalp hair loss;
- priapism (few cases reported);
- skin necrosis (few cases reported), toxic skin eruption (Stevens-Johnson syndrome) and angiodema;
- hyperkalaemia due to hypoaldosteronism (especially in patients with renal impairment and diabetes mellitus);
- osteoporosis (related to long term treatment)

There are two case reports of serious adverse drug reactions for Innohep®: one subdural haematoma and one retroperitoneal haemorrhage. One case of metrorrhagia has been reported.

Note: Due to the sodium metabisulfite content, hypersensitivity reactions can occur in individual cases, especially in patients who have bronchial asthma. This may be expressed as vomiting, diarrhoea, dyspnoea, acute asthmatic attack, disturbance of consciousness or collapse and shock.

INTERACTIONS

Concomitant use of medication with an effect on haemostasis, such as aspirin/ASA, and other non-steroidal anti-inflammatory drugs, dipyridamole, thrombolytic agents, activated protein C, direct factor Xa and IIa inhibitors, vitamin K antagonists and Dextran, may enhance the anticoagulant effect of Innohep®. Such concomitant usage should be avoided or carefully monitored.

A decrease in the efficacy of heparin is exhibited due to its interaction with nitroglycerine. This interaction should not be ruled out for tinzaparin.

Drugs that increase the serum potassium concentration should only be taken concomitantly under especially careful medical supervision.

OVERDOSAGE

Overdosage of Innohep® may be complicated by haemorrhage. Due to the relatively short half-life of Innohep® (see PHARMACOKINETICS), minor haemorrhages can be managed conservatively following treatment discontinuation. In recommended dosages there should be no need for an antidote but in the event of accidental administration of an overdose, the effect of Innohep® can be reversed by intravenous administration of 1% protamine sulphate solution. Patients should be carefully monitored following antidote administration.

The dose of protamine sulphate required for neutralisation should be accurately determined by titrating with patient’s plasma. As a rule, 1mg of protamine sulphate neutralises the effect of 100 anti-Xa IU tinzaparin. The anti-Xa activity of tinzaparin is only partially neutralised by protamine sulphate and the anti-Xa and anti-IIa Activated Partial Thromboplastin Time (APTT) activities are seen to return 3 hours after its reversal.

It is recommended that protamine sulphate (1 mg/100 anti-Xa IU of tinzaparin) should be given as intermittent intravenous injections or continuous infusion. Potential side-effects of protamine sulphate must be considered and patients carefully observed. Note that protamine should only be used in emergency situations as it has an anti-coagulant effect in itself and it may cause an anaphylactoid reaction.

Transfusion of fresh plasma may be used, if necessary.

During management of all low molecular weight heparin overdose situations, plasma anti-factor Xa and anti-factor IIa should be measured.
PHARMACEUTICAL PRECAUTIONS

Shelf life 2 years

Storage Conditions Store below 25°C.

PACKAGING QUANTITIES

<table>
<thead>
<tr>
<th>Presentations</th>
<th>Concentration of Anti-Xa (IU/mL)</th>
<th>Volume (mL)</th>
<th>Number of Syringes/Vials per pack</th>
<th>Total Dose (anti-Xa IU)</th>
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<tr>
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MEDICINE CLASSIFICATION

Prescription Only Medicine.

FURTHER INFORMATION

Nil

NAMES AND ADDRESSES

Manufactured by:
LEO Pharma A/S
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