

## DATA SHEET (Marketed)

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

### PRESENTATION

Innohep<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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).

### USES

#### **ACTIONS**

Innohep<sup>®</sup> 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<sup>®</sup> are monitored by anti-Xa activity. Innohep<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> per litre.

### ***Treatment of pulmonary embolism:-***

Single daily subcutaneous injection of 175 anti-Xa IU/kg.

### ***Liver and Kidney Insufficiency:-***

Innohep<sup>®</sup> 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<sup>®</sup> is contraindicated in patients with:

- known hypersensitivity to fractionated or unfractionated heparins, or any of the other constituents;
- haemorrhagic disorders;
- an actual or potential bleeding site, e.g. peptic ulcer; uncontrolled severe hypertension; septic endocarditis;
- a current history of heparin-associated thrombocytopenia (type II);
- intracranial or intraocular bleeding or other current active bleeding process;
- surgery involving the brain, spinal cord or eye;
- lumbar puncture, spinal or epidural anaesthesia;
- severe impairment of the liver, kidney or pancreas;
- haemorrhagic stroke, cerebral aneurysm;
- retinopathy or vitreous haemorrhage;
- threatened abortion;

## **WARNINGS AND PRECAUTIONS**

Innohep<sup>®</sup> should **not** be administered:

- by intramuscular injection due to the risk of haematoma;
- 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<sup>®</sup> contains sodium bisulfite.

Innohep<sup>®</sup> 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;

Platelet counts are recommended: before administration of Innohep<sup>®</sup>, on the first day of therapy and then regularly every 3 or 4 days, and at the end of therapy.

Precaution is recommended in the treatment of patients with severe renal impairment (creatinine clearance < 30 mL/min).

Precaution is recommended in the treatment of elderly patients with renal impairment. Renal function in elderly patients should be assessed, and in patients with severe renal impairment (creatinine clearance < 30 mL/min) monitoring of anti-factor Xa activity should be considered

There is no experience with the use of Innohep<sup>®</sup> in the treatment of children.

Regarding the ability of those receiving treatment to drive or use machinery, Innohep<sup>®</sup> is presumed to be safe or unlikely to produce an effect.

## ***Pregnancy and Lactation***

Pregnancy: Category B1

Data on a limited number (637) of exposed pregnancies indicate no additional risk of tinzaparin on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. No transplacental passage was demonstrated in two clinical studies. Animal data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing tinzaparin to pregnant women.

### **Pregnant patients with prosthetic heart valves**

Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant 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). The 2 mL vial of Innohep<sup>®</sup> 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<sup>®</sup> formulations containing benzyl alcohol is not recommended during pregnancy.

It is not known whether Innohep<sup>®</sup> is excreted in breast milk.

## **ADVERSE EFFECTS**

### **Frequent: $\geq 1/100$ and $< 1/10$ ( $\geq 1\%$ and $< 10\%$ )**

- bleeding complications (skin, mucous membrane, wounds, gastrointestinal, urogenital); as for conventional heparin. However, at the recommended dose this risk is low;
- increase in serum potassium concentration;
- increase in gamma-glutamyltransferase (GGT), lactodehydrogenase (LDH), lipase;
- injection site haematoma and pain;
- As for conventional heparin, a transient increase in aminotransferase levels is frequently observed. Cessation of treatment is not usually required.

### **Rare: $\geq 1/10,000$ and $< 1/1000$ ( $\geq 0.01\%$ and $< 0.1\%$ )**

- cases of severe antibody-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;
- anaphylactoid reactions; anaphylactic shock, allergic reactions with symptoms such as nausea, vomiting, fever, headache, urticaria, pruritus, dyspnoea, bronchospasm, hypotension;
- transient scalp hair loss;
- skin rashes and minor bruising at the site of injection;
- priapism (few cases reported);
- skin necrosis (few cases reported).

In **very rare** cases, hypoadosteronism, associated with hyperkalaemia and metabolic acidosis (especially in patients with renal impairment and diabetes mellitus) has occurred.

There are two case reports of serious adverse drug reactions for Innohep<sup>®</sup>: 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 medication with an effect on haemostasis, such as aspirin/ASA, NSAIDs, dipyridamole, vitamin K antagonists and Dextran, may enhance the anticoagulant effect of Innohep<sup>®</sup>.

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<sup>®</sup> may be complicated by haemorrhage. 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<sup>®</sup> can be reversed by intravenous administration of 1% protamine sulphate solution.

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**

<b>Presentations</b>	<b>Concentration of Anti-Xa (IU/mL)</b>	<b>Volume (mL)</b>	<b>Number of Syringes/ Vials per pack</b>	<b>Total Dose (anti-Xa IU)</b>
Innohep <sup>®</sup> unit-dose prefilled syringe	10,000	0.45	10	4500
Innohep <sup>®</sup> unit-dose prefilled syringe	20,000	0.50	2	10,000
Innohep <sup>®</sup> unit-dose prefilled syringe	20,000	0.70	2	14,000
Innohep <sup>®</sup> unit-dose prefilled syringe	20,000	0.90	2	18,000
Innohep <sup>®</sup> vial	20,000	2.00	10	40,000

## **MEDICINE CLASSIFICATION**

Prescription Only Medicine.

## **FURTHER INFORMATION**

Nil

## **NAMES AND ADDRESSES**

### **Manufactured by:**

Leo Pharmaceutical Products Ltd A/S  
55 Industriparken  
DK-2750 Ballerup  
DENMARK

### **Distributed in New Zealand by:**

CSL Biotherapies (NZ) Limited  
666 Great South Road  
Penrose, Auckland  
NEW ZEALAND

Free Phone 0800 502 757  
Free Fax 0800 920 054

Phone 09 579 8105  
Fax 09 579 8106

## **DATE OF PREPARATION**

October 2009

Innohep<sup>®</sup> is a registered trademark of Leo Pharmaceutical Products Ltd. A/S