innohep® Anticoagulant

Tinzaparin sodium

For subcutaneous injection

10 Vials of 2 ml
Tinzaparin sodium 10,000 IU anti-Xa/ml, preserved with benzyl alcohol (10 mg/ml).
Tinzaparin sodium 20,000 IU anti-Xa/ml, preserved with benzyl alcohol (10 mg/ml), stabilized with sodium metabisulphite.

10 Pre-filled syringes with needle safety device of 0.25ml, 0.35ml or 0.45ml
Tinzaparin sodium 10,000 IU anti-Xa/ml.

2 Pre-filled syringes with needle safety device of 0.5ml, 0.7ml or 0.9ml
Tinzaparin sodium 20,000 IU anti-Xa/ml, stabilized with sodium metabisulphite.

Properties
Tinzaparin sodium is a low molecular weight heparin produced by enzymatic depolymerization of conventional heparin.
The molecular mass is between 1,000 and 14,000 dalton, with a weight average molecular mass of approx. 6,500 dalton. Tinzaparin sodium is an anti-thrombotic agent. **innohep®** has a bioavailability of about 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 3.7 hours. Tinzaparin sodium is eliminated, primarily with the urine, as unchanged drug.

The pharmacokinetics/pharmacodynamics of **innohep®** are monitored by anti-Xa activity. There is a linear dose-response relationship between plasma activity and the dose administered.

The biological activity of **innohep®** is expressed in international units anti-Xa.

Indications
Treatment of deep-vein thrombosis and pulmonary embolism.
Prevention of postoperative deep-vein thrombosis in patients undergoing general and orthopaedic surgery.
Prevention of clotting in in-dwelling intravenous lines for extracorporeal circulation and haemodialysis.

Dosage
Treatment of DVT and PE:
The recommended dose is 175 IU anti-Xa/kg body-weight s.c. once daily.

Thromboprophylaxis in patients with moderate risk of thrombosis (general surgery):
On the day of operation 3,500 IU anti-Xa s.c. 2 hours before surgery and postoperatively once daily 3,500 IU anti-Xa for 7–10 days.

Thromboprophylaxis in patients with high risk of thrombosis (e.g. total hip replacement):
On the day of operation 4,500 IU anti-Xa s.c. 12 hours before surgery or 50 IU anti-Xa/kg body-weight s.c. 2 hours before surgery and then once daily until the patient has been mobilized.

For short-term haemodialysis (less than 4 hours):
A bolus dose of 2,000–2,500 IU anti-Xa into the arterial side of the dialyser (or intravenously) at the beginning of dialysis.

Long-term haemodialysis (more than 4 hours):
A bolus dose of 2,500 IU anti-Xa into the arterial side of the dialyser (or intravenously) at the beginning of dialysis, followed by an infusion of 750 IU anti-Xa /hour.

Dose adjustment: Increase or decrease of the bolus dose, if required, can be made in steps of 250–500 IU anti-Xa until a satisfactory response is obtained.

Elderly:
Renal function should be assessed with e.g. the Cockcroft-Gault formula to estimate creatinine clearance levels.
No dose reduction is needed in elderly patients with normal renal function. (See **Special precautions**).

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 **Special precautions**).

Overdose
Haemorrhage is the main complication of overdose. Due to the relatively short half-life of **innohep®** minor haemorrhages can be managed conservatively following treatment discontinuation. Serious haemorrhage may require the administration of the antidote protamine sulphate. Patients should be carefully monitored.

Undesirable effects
The most frequently reported undesirable effects are haemorrhage events, anaemia secondary to haemorrhage and injection site reactions.

Haemorrhage may present in any organ and have different degrees of severity. Complications may occur particularly when high doses are administered. Although major haemorrhages are uncommon, death or permanent disability has been reported in some cases.

Immune-mediated 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. Immune-mediated heparin-induced thrombocytopenia (type II) may be associated with arterial and venous thrombosis. **innohep®** must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia (see Special warnings and precautions).

In rare cases, **innohep®** may cause hyperkalaemia due to hypoaldosteronism. Patients at risk include those with diabetes mellitus or renal impairment (see Special warnings and precautions).

Serious allergic reactions may sometimes occur. These include rare cases of skin necrosis, toxic skin eruption (e.g. Stevens-Johnson syndrome), angioedema and anaphylaxis. Treatment should be promptly discontinued at the slightest suspicion of such severe reactions.

Very common ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000

Blood and lymphatic system disorders	
Common ≥1/100 and < 1/10	Anaemia (incl. haemoglobin decreased)
Uncommon ≥1/1,000 and <1/100	Thrombocytopenia (type I) (incl. platelet count decreased)
Rare ≥1/10,000 and <1/1,000	Heparin-induced thrombocytopenia (type II) Thrombocytosis
Immune system disorders	
Uncommon ≥1/1,000 and <1/100	Hypersensitivity
Rare ≥1/10,000 and <1/1,000	Anaphylactic reaction
Metabolism and nutrition disorders	
Rare ≥1/10,000 and <1/1,000	Hyperkalaemia
Vascular disorders	
Common ≥1/100 and < 1/10	Haemorrhage Haematoma
Uncommon ≥1/1,000 and <1/100	Bruising, ecchymosis and purpura
Hepatobiliary disorders	
Uncommon ≥1/1,000 and <1/100	Hepatic enzyme increased (incl. increased transaminases, ALT, AST and GGT)
Skin and subcutaneous tissue disorders	
Uncommon ≥1/1,000 and <1/100	Dermatitis (incl. dermatitis allergic and bullous) Rash Pruritus
Rare ≥1/10,000 and <1/1,000	Toxic skin eruption (including Stevens-Johnson syndrome) Skin necrosis Angioedema Urticaria
Musculoskeletal and connective tissue disorders	
Rare ≥1/10,000 and <1/1,000	Osteoporosis (in connection with long-term treatment)
Reproductive system and breast disorders	
Rare ≥1/10,000 and <1/1,000	Priapism
General disorders and administration site conditions	
Common ≥1/100 and < 1/10	Injection site reaction (incl. injection site haematoma, haemorrhage, pain, pruritus, nodule, erythema and extravasation)

Effects on ability to drive and use machines
innohep® has no or negligible influence on the ability to drive or use machines.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Current or history of immune-mediated heparin-induced thrombocytopenia (type II) (see Special warnings and precautions for use).
Active major haemorrhage or conditions predisposing to major haemorrhage.
Major haemorrhage is defined as fulfilling any one of these three criteria:
a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine 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.

Septic endocarditis.

For vials only
*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.*

For treatment indications only
Treatment doses of **innohep®** (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia. If neuraxial anaesthesia is planned, **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.

Special warnings and precautions for use

Neuraxial anaesthesia

Caution is advised when administering **innohep®** to patients at risk of haemorrhage. For patients at risk of major haemorrhage see Contraindications. The combination with medicinal products affecting platelet function or the coagulation system should be avoided or carefully monitored (see Interaction with other medicinal products and other forms of interaction).

Intramuscular injections
innohep® should not be administered by intramuscular injection due to the risk of haematoma.
Due to the risk of haematoma, concomitant intramuscular injections should also be avoided.

Heparin-induced thrombocytopenia
Because of the risk of immune-mediated heparin-induced thrombocytopenia (type II), platelet count should be measured before the start of treatment and periodically thereafter. **innohep®** must be discontinued in patients who develop immune-mediated heparin-induced thrombocytopenia (type II) (see Contraindications and Undesirable effects). Platelet counts will usually normalise within 2 to 4 weeks after withdrawal.

Hyperkalaemia
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 if **innohep®** treatment is considered lifesaving (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance).

Prosthetic heart valves
There have been no adequate studies to assess the safe and effective use of **innohep®** in preventing valve thrombosis in patients with prosthetic heart valves. The use of **innohep®** cannot be recommended for this purpose.

Renal impairment
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/minute). Caution is recommended when treating patients with severe renal impairment (creatinine clearance < 30 ml/minute). There is limited data available in patients with an estimated creatinine clearance level below 20 ml/minute.

Elderly
Elderly are more likely to have reduced renal function, (see Renal impairment); therefore caution should be exercised when prescribing **innohep®** to the elderly.

Excipients warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

The multidose vial formulations of **innohep®** contain 10 mg/ml of the preservative benzyl alcohol. Benzyl alcohol may cause toxic and anaphylactoid reactions in infants and children up to 3 years old.

Some formulations of **innohep®** contain sodium metabisulphite. Metabisulphites may rarely cause severe hypersensitivity reactions and bronchospasm. **innohep®** formulations containing sodium metabisulphite must be used with caution in patients with asthma.

The 20,000 IU anti-Xa/ml formulation of **innohep®** contains sodium metabisulphite, which may cause allergic reactions, including anaphylaxis in predisposed patients. In the remaining formulations without sulphite, this risk does not exist.

Interactions with other medicinal products and other forms of interaction
The anticoagulant effect of **innohep®** may be enhanced by other drugs affecting the coagulation system, such as those inhibiting platelet function (e.g. acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs), thrombolytic agents, vitamin K antagonists, activated protein C, direct factor Xa and IIa inhibitors. Such combinations should be avoided or carefully monitored (see Special warnings and precautions for use).

Use during Pregnancy and Lactation
Data from sequential pharmacokinetic monitoring in 55 pregnancies suggest that pharmacokinetic properties of tinzaparin do not differ from the non-pregnant state.

Pregnancy
Anticoagulant treatment of pregnant women requires specialist involvement.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

A large amount of data on pregnant women (more than 2,200 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity of tinzaparin. Tinzaparin does not cross the placenta. **innohep®** can be used during all trimesters of pregnancy if clinically needed.

Epidural anaesthesia:
Due to the risk of spinal haematoma, treatment doses of **innohep®** (175 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®**. Prophylactic doses may be used as long as a minimum delay of 12 hours is allowed between the last administration of **innohep®** and the needle or catheter placement.

Pregnant women with prosthetic heart valves:
Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of **innohep®** and other low molecular weight heparins. **innohep®** cannot be recommended for use in this population.

Excipients
innohep® vials contain benzyl alcohol. As this preservative may cross the placenta,

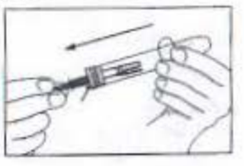
Animal data indicate that **innohep®** excretion into breast milk is minimal.
It is unknown whether tinzaparin is excreted into human milk. Although oral absorption of low molecular weight heparins is unlikely, a risk to newborns/infants cannot be excluded.
In patients at risk, the incidence of venous thromboembolism is particularly high during the first six weeks after child birth.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from **innohep®** therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no clinical studies with **innohep®** regarding fertility.

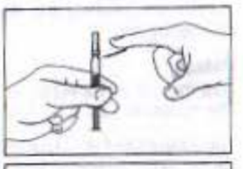
Incompatibilities
innohep® is compatible with isotonic sodium chloride (9 mg/ml) or isotonic glucose (50 mg/ml). It should not be admixed with other infusion fluids.

Instructions for use of the innohep® syringes:
Thoroughly wash your hands before you inject this medicine. Wipe clean the skin around the injection site with a surgical alcohol pad and let it dry – do not rub.

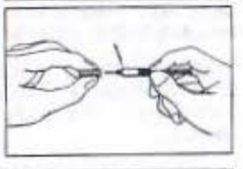
1. Open the tube bending the coloured lid all the way back and take out the syringe. Inspect the content of the syringe before you use it. If you observe cloudiness or precipitate in the medicine, do not use it but take another syringe. The medicine may turn yellow during storage but can still be used if the solution is clear and expiry date is not overdue. Each syringe is intended to be used only once.



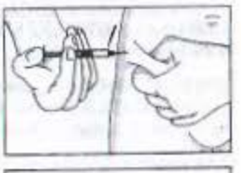
2. Bend the safety device down away from the protective cap on the needle



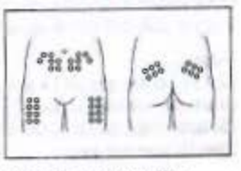
3. Remove the protective needle cap without bending the needle. Do not pull back the plunger and do not press out the air bubble. If the air bubble is not placed right by the plunger, then tap lightly on the syringe until the air bubble is in place.



4. Hold a skin fold loosely between thumb and index finger of one hand and with the other hand slowly insert the needle vertically at the skin fold, i.e. at a right angle to the skin.



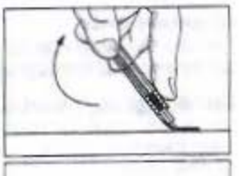
5. Slowly inject the required dose into the fatty tissue of e.g. the abdominal skin, the extensor sides of the thigh, lower back or upper arm. Wait a few seconds to give the solution time to distribute before you remove the needle and release the skin fold.

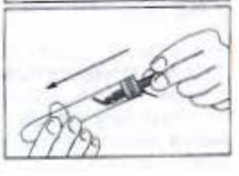


6. Wipe off any blood with a tissue. Choose a different injection site next time (for instance, move from the left to the right of the abdomen).

7. Bend the safety device back to its original position so it is now underneath the needle. Then with the safety device flat against a hard surface, push downwards until the needle locks into the device.

8. You can either place the used syringe in the tube with the needle downwards or you can put the used syringe into a sharps container. The syringe is now secured, and the tube or sharps container can be handed over for destruction at the hospital or by the pharmacist.





Storage condition
Do not store above 30°C.

Shelf life
Multidose Vials: 2 years.
Pre-filled Syringes: 3 years.

This leaflet was last revised in June 2014

LEO Pharma A/S – Ballerup – Denmark

L E O

LEO
032128-00