LEO®

PRODUCT MONOGRAPH

Prinnohep®

tinzaparin sodium

Sterile solution for SC injection

10,000 anti-Xa IU/mL and 20,000 anti-Xa IU/mL

Ph. Eur.

Anticoagulant / Antithrombotic

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PrINNOHEP®

tinzaparin sodium

PART I : HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous injection	Sterile solution for injection: **10,000 anti-Xa IU/mL:** Prefilled safety syringes* (preservative free): 2,500 IU†/0.25 mL; 3,500 IU/0.35mL and 4,500 IU/0.45 mL Multi-dose vial (with preservative): 20,000 IU/2 mL **20,000 anti-Xa IU/mL:** Prefilled safety syringes* (preservative free): 8,000 IU/0.4 mL; 10,000 IU/0.5 mL; 12,000 IU/0.6 mL; 14,000 IU/0.7 mL; 16,000 IU/0.8 mL; 18,000 IU/ 0.9 mL Multi-dose vial (with preservative): 40,000 IU/2 mL	The multidose vial contains sodium metabisulphite and benzyl alcohol. The 8,000 IU, 10,000 IU, 12,000 IU, 14,000 IU, 16,000 IU and 18,000 IU pre-filled syringes contain sodium metabisulfite *For a complete listing see Dosage Forms, Composition and Packaging section.*

*Pre-filled safety syringes have a 27-gauge, ½ inch needle. All formats are latex free.

† anti-Xa IU abbreviated as IU

INDICATIONS AND CLINICAL USE

INNOHEP (tinzaparin sodium) is indicated for:

- The prevention of postoperative venous thromboembolism in patients undergoing orthopaedic surgery and in patients undergoing general surgery who are at high risk of developing postoperative venous thromboembolism (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).
- The treatment of deep vein thrombosis and/or pulmonary embolism.
- The prevention of clotting in indwelling intravenous lines for haemodialysis and

extracorporeal circulation in patients without high bleeding risk.

INNOHEP can not be used interchangeably, unit for unit, with unfractionated heparin or other low molecular weight heparins (LMWHs) (see WARNINGS AND PRECAUTIONS, General).

Geriatrics: For elderly patients over 70 years of age with renal impairment, refer to WARNINGS AND PRECAUTIONS, Geriatrics. Close monitoring of elderly patients with low body weight (e.g., < 45 kg) and those predisposed to decreased renal function is recommended**.** (see WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics: The safety and effectiveness of INNOHEP in children has not been established.

CONTRAINDICATIONS

- Hypersensitivity to INNOHEP (tinzaparin sodium); or any of its constituents, including benzyl alcohol (when using multi-dose vials) or sodium metabisulphite (see WARNINGS AND PRECAUTIONS); or to other LMWHs and/or heparin
- The multi-dose vials of INNOHEP contain 10 mg/mL benzyl alcohol as preservative and **must not** be given to children <2 years old, premature infants and neonates, due to the risk of developing gasping syndrome.
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), or in patients in whom an *in vitro* platelet-aggregation test in the presence of tinzaparin is positive
- Acute or subacute septic endocarditis
- Generalized haemorrhage tendency and other conditions/diseases involving an increased risk of haemorrhage (e.g. severe liver insufficiency, women with abortus imminens)
- Haemophilia or major blood clotting disorders
- Acute cerebral insults or haemorrhagic cerebrovascular accidents (except if there are systemic emboli)
- Active bleeding from a local lesion such as an acute ulcer (e.g., gastric or duodenal) or ulcerating carcinoma
- Uncontrolled severe hypertension
- Diabetic or haemorrhagic retinopathy
- Injury or surgery involving the brain, spinal cord, eyes or ears

- Spinal/epidural anaesthesia requiring treatment dosages of INNOHEP (175 IU/kg once daily) due to an increased risk of bleeding

WARNINGS AND PRECAUTIONS

General

INNOHEP (tinzaparin sodium) must NOT be administered by intramuscular injection due to risk of hematoma.

Due to the increased risk of bleeding, concomitant medications should not be given by intramuscular injection and care should be taken when giving lumbar puncture and similar procedures.

INNOHEP should be used with caution in patients receiving oral anticoagulants, NSAIDs, platelet inhibitors and thrombolytic agents because of increased risk of bleeding.

INNOHEP cannot be used interchangeably (unit for unit) with unfractionated heparin or other LMWHs as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units and dosages. Special attention and compliance with instructions for use of each specific product is required during any change in treatment.

Determination of peak anti-Xa activity in plasma at 4-6 hours post-dosing is the only method available for monitoring tinzaparin levels. Routine clotting assays are not suitable for monitoring tinzaparin anticoagulant activity. APTT prolongation is not a suitable test for monitoring the LMWHs (see Monitoring and Laboratory Tests and ACTION AND CLINICAL PHARMACOLOGY).

Cardiovascular

Use in Patients with Prosthetic Heart Valves: Cases of prosthetic valve thrombosis have been reported in patients who received LMWHs for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see Special Populations, Pregnant Women).

Gastrointestinal

INNOHEP should be used with caution in patients with a history of gastrointestinal ulceration.

Hematologic

INNOHEP should not be used for the treatment of pulmonary embolism in patients with severe haemodynamic instability.

Hemorrhage: Bleeding may occur in conjunction with unfractionated heparin or LMWH use. As with other anticoagulants, INNOHEP should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with INNOHEP. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site (see ADVERSE REACTIONS, Bleeding).

Post-Surgical Bleeding: As with all antithrombotic agents, there is a risk of systemic bleeding with INNOHEP. Care should be taken with INNOHEP use in high dose treatment of newly operated patients. In the event of excessive blood loss from the surgical wound, the first injection of INNOHEP should be deferred until the bleeding has stopped.

After treatment is initiated, patients should be carefully monitored for bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical drain and periodic measurements of haemoglobin and anti-Xa determinations.

In the case of minor bleeding, the drug should be postponed or withdrawn. When serious bleeding requires reversal of INNOHEP, protamine sulphate (1% solution) by slow infusion will largely neutralize INNOHEP (see OVERDOSAGE). The effect of protamine sulphate should be monitored by the APTT.

Thrombocytopenia: Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of INNOHEP.

Platelets: Platelet counts should be measured before the start of treatment and periodically thereafter. Regular monitoring of platelet counts also applies to extended treatment for cancer associated thrombosis.

Caution is recommended when administering INNOHEP to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During INNOHEP administration, special caution is necessary in rapidly developing thrombocytopenia and severe thrombocytopenia (<100,000/mcL). A positive or indeterminate result obtained from *in vitro* tests for antiplatelet antibody in the presence of tinzaparin or other LMWHs and/or heparin would contraindicate INNOHEP.

Thrombocytosis: As with other LMWHs, the administration of INNOHEP in some patients undergoing surgical procedures (especially orthopaedic) or having a concomitant inflammatory process has coincided with an asymptomatic increase in platelet count. If an increase in platelet count occurs INNOHEP should be stopped, the benefit of continuing therapy for that patient should be re-evaluated against the risk. Drugs affecting platelet function or the coagulation system should in general not be given concomitantly with INNOHEP.

Hepatic

INNOHEP should be used with caution in patients with hepatic insufficiency.

Immune

Sulphite Sensitivity: The overall prevalence of sulphite sensitivity in the general population is unknown. Sulphite sensitivity is seen more frequently in asthmatics than in non-asthmatic people. Sodium metabisulphite, which may cause allergic reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people, is present in INNOHEP multi-dose vials (10,000 and 20,000 anti-Xa IU/mL) and INNOHEP 20,000 anti-Xa IU/mL unit-dose graduated syringes (8,000 IU/syringe to 18,000 IU/syringe). However, INNOHEP 10,000 anti-Xa IU/mL unit-dose syringes (2,500 IU/syringe, 3,500 IU/syringe and 4,500 IU/syringe) do not contain sodium metabisulphite.

Metabolic

All unfractionated heparins/LMWHs can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting INNOHEP therapy and monitored regularly thereafter especially if treatment is prolonged beyond 7 days.

Peri-Operative Considerations

Spinal/Epidural Hematomas: There have been cases of intra-spinal haematomas with the concurrent use of LMWH and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. The risk of these events may be higher with the use of post-operative indwelling epidural catheters or by the concomitant use of drugs affecting haemostasis: non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other drugs affecting coagulation. The risk also appears to be increased by traumatic or repeated epidural or spinal procedure. **INNOHEP should only be used concurrently with spinal/epidural anaesthesia when the therapeutic benefits to the patient outweigh the possible risks (see CONTRAINDICATIONS).** When used concurrently, no spinal invasion should be performed for 12 hours following the dose of LMWH and the next dose should be held until at least 2 hours after the anaesthesia procedure. The same rules apply to the withdrawal or manipulation of the catheter. Careful vigilance for neurological signs is recommended, with rapid diagnosis and treatment; if such signs occur (see ADVERSE REACTIONS, Bleeding).

Selection of General Surgery Patients: General surgery patients, who have one or more of the following risk factors, are at high risk of developing postoperative venous thromboembolism: previous venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of lower limb, bed rest more than 5 days prior to surgery, predicted duration of surgery more than 30 minutes, and age 60 years or above.

Renal

INNOHEP should be used with caution in patients with moderate to severe renal impairment. In all cases of impaired renal function, patients should be closely monitored.

In patients being treated with tinzaparin sodium (175 IU/kg) for deep vein thrombosis (DVT), a population pharmacokinetic (PK) analysis determined that tinzaparin sodium clearance based on anti-Xa activity was related to creatinine clearance calculated by Cockcroft-Gault equation. In this PK analysis, a reduction in tinzaparin sodium clearance in moderate (30-50 mL/min) and severe (<30 mL/min) renal impairment was observed. Patients with severe renal impairment exhibited a reduction in tinzaparin sodium clearance relative to patients with normal renal function (>80 mL/min).

Special Populations

Pregnant Women: The 2 mL multi-dose vials of INNOHEP (10,000 anti-Xa IU/mL and 20,000 anti-Xa IU/mL) contain 20 mg of benzyl alcohol as a preservative (10 mg of benzyl alcohol per mL). Cases of fatal "Gasping Syndrome" have been reported in the literature, which occurred in premature infants and neonates when large amounts (99-404 mg/kg/day) of benzyl alcohol have been administered. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Therefore the multi-dose vials of INNOHEP preserved with benzyl alcohol must not be used in children <2 years old, newborn and preterm babies (see CONTRAINDICATIONS). Because benzyl alcohol may cross the placenta, this formulation should also not be used in pregnant women. Prefilled syringes of INNOHEP do not contain benzyl alcohol.

The use of INNOHEP in women with abortus imminens is contraindicated (see CONTRAINDICATIONS).

Teratogenic effects: As with other LMWHs, INNOHEP should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWH during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic displasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic effects: There have been post-marketing reports of fetal death when pregnant women received LMWH. Causality for these cases has not been established. Pregnant women

receiving anticoagulants, including INNOHEP, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving INNOHEP should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if INNOHEP is administered during pregnancy.

Prosthetic valve thrombosis: There are also post-marketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving LMWHs for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of LMWHs or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

Nursing Women: It is not known whether INNOHEP is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when INNOHEP is administered to nursing women.

Pediatrics: The safety and effectiveness of INNOHEP in children has not been established.

Geriatrics: INNOHEP is not recommended in elderly (>70 years) patients with renal impairment. Elderly patients receiving LMWHs are at increased risk of bleeding. Careful attention to dosing and concomitant medications, especially anti-platelet preparations, is advised. Renal function should be assessed and patients with renal impairment and those with low body weight (e.g., <45 kg) should be monitored. Since renal function declines with age, elimination of tinzaparin sodium may be reduced in elderly patients. INNOHEP should be used with care in these patients (see Human Studies, IRIS).

Patients with Extreme Body Weight: Safety and efficacy of LMWHs in high weight (e.g., > 120 kg) and low weight (e.g., < 45 kg) patients has not been fully determined. Individualised clinical and laboratory monitoring is recommended in these patients.

Monitoring and Laboratory Tests

INNOHEP has only a moderate prolonging effect on clotting time assays such as APTT or thrombin time. Clinically meaningful prolongation of APTT during hemodialysis or treatment of acute deep vein thrombophlebitis with INNOHEP should only be used as an indication of overdosage.

INNOHEP is administered subcutaneously and therefore the individual patient's anti-Xa activity level will not remain within the range that would be expected with unfractionated heparin by continuous intravenous infusion throughout the entire dosing interval. In clinical studies the median peak plasma anti-Xa levels achieved approximately 4 hours after subcutaneous administration of 3500 IU, 75 IU/kg or 175 IU/kg were 0.15, 0.34 and 0.70 anti-Xa IU/mL respectively. INNOHEP should be administered as directed (see DOSAGE AND ADMINISTRATION).

With normal prophylactic doses, INNOHEP does not modify global clotting tests of activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin clotting time (TT). Therefore, treatment cannot be monitored with these tests.

Periodic complete blood counts including platelet count and haematocrit or haemoglobin, and stool test for occult blood are recommended during treatment with INNOHEP. When administered at the recommended treatment doses, routine anticoagulation tests such as PT and APTT are relatively insensitive measures of INNOHEP activity, and therefore, are unsuitable for monitoring.

The measurements of anti-Xa and anti-IIa activities in plasma serve as surrogates for the concentrations of molecules which contain the high-affinity binding site for antithrombin. Monitoring patients based on anti-Xa activity is generally not advised.

Renal function should be assessed with Cockcroft-Gault formula to estimate creatinine clearance level.

Since INNOHEP use may be associated with a rise in hepatic transaminases, this observation should be considered when liver function tests are assessed (see ADVERSE REACTIONS, Hepatobiliary Disorders).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Based on reporting from clinical trials, bleeding and injection site reactions (such as irritation, pain and ecchymosis) are the most common side effects with INNOHEP (tinzaparin sodium).

Bleeding: As with any antithrombotic treatment, haemorrhagic manifestations can occur. Injection site haematomas are a common side effect with INNOHEP, occurring at a frequency of 5% or less with lower (prophylaxis) doses to 10% or more with higher (treatment) doses.

The incidence of major haemorrhagic complications during INNOHEP treatment has been low and generally did not differ from that observed with unfractionated heparin. In clinical trials, the definition of major bleeding included; bleeding accompanied by ≥2 g/dl decrease in haemoglobin, requiring transfusion of two or more units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint. Results from pivotal clinical trials for each indication are provided in Table 1.

Patients taking INNOHEP are at risk for major bleeding complications when the plasma anti-Xa levels approach 2.0 IU/mL. Other risk factors associated with bleeding on therapy with heparins include a serious concurrent illness, chronic heavy alcohol consumption, use of platelet inhibiting drugs, renal failure, age and possibly, the female gender. Petechiae or easy bruising may precede frank haemorrhage. Bleeding may range from minor local haematoma or major haemorrhage. Haemorrhage can lead to anemia. The early signs of bleeding may include epistaxis, haematuria, or melena. Bleeding may occur at any site and may be difficult to detect, such as retroperitoneal bleeding. Bleeding may also occur from surgical sites. Major hemorrhage, including retroperitoneal or intracranial bleeding, has been reported in association with INNOHEP use, in some cases leading to fatality.

There have been cases of intraspinal haematomas with the concurrent use of LMWH and spinal/epidural anaesthesia resulting in long term or permanent paralysis (incidence 1: 45,000) (see WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).

Table 1. Major Bleeding Events in Clinical Trials for Treatment of Acute DVT and/or PE, DVT Prophylaxis, and Haemodialysis[1]

Indication	Treatment Group (bleeding frequency %)	
Treatment of Acute DVT (with or without PE)	INNOHEP, N=213	Heparin, N=219
	0.5 [2]	5.0 [2]
Treatment of PE	INNOHEP, N=304	Heparin, N=308
	1.0 [3]	1.6 [3]
Prevention of Postoperative DVT in Orthopaedic Surgery	INNOHEP[4], N=715	Warfarin[4], N=721
	2.8 [5]	1.2 [5]
Haemodialysis	INNOHEP[6], N=73	Dalteparin[6], N=76
	1.4	1.3

1 Bleeding accompanied by ≥ 2 gram/dL decline in hemoglobin, requiring transfusion of 2 or more units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint.

2 INNOHEP 175 IU/kg once daily SC. Unfractionated heparin initial IV bolus of 5,000 IU followed by continuous IV Infusion adjusted to an aPTT of 1.5 to 2.5 followed by continuous IV infusion adjusted to an aPTT of 2.0 to 3.0 In all groups treatment continued for approximately 6 to 8 days, and all patients received oral anticoagulant treatment commencing in the first 2 to 3 days ($p<0.01$).

3 INNOHEP 175 IU/kg once daily SC. Unfractionated heparin initial IV bolus of 50 IU/kg followed by continuous IV infusion adjusted to an aPTT of 2.0 to 3.0 In all groups treatment continued for approximately 6 to 8 days, and all patients received oral anticoagulant treatment commencing in the first 2 to 3 days.

4 INNOHEP 75 IU/kg once daily SC starting 18-24 hours post-surgery. Warfarin starting at 10 mg on the evening post-surgery and dose adjusted to maintain an INR of 2.0 to 3.0. In all groups treatment continued until 14 days post-surgery or until hospital discharge if this occurred earlier.

5 The 95% CI on the difference in major bleeding event rates (-1.6%) was -3.0%, -0.1%.

6 Bolus dose into arterial side of dialyzer immediately prior to start of dialysis. INNOHEP 4,500 IU for dialyses ≤4 hours or 6,700 IU for dialyses >4 hours. Dalteparin 5,000 IU for dialyses ≤4 hours or 35 IU/kg plus 12 IU/kg/hour for dialyses >4 hours.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events with INNOHEP or heparin reported at a frequency of ≥1% in clinical trials with patients undergoing treatment for proximal DVT and/or PE are provided in Table 2.

Table 2. Adverse Events Occurring in ≥1% of Patients During Treatment of Acute Deep Vein Thrombosis and/or PE

	Treatment Group [1]	
Adverse Event	**INNOHEP N=519 n (%)**	**Heparin N=524 n (%)**
Urinary Tract Infection	19 (3.7%)	18 (3.4%)
Chest Pain	12 (2.3%)	8 (1.5%)
Epistaxis	10 (1.9%)	7 (1.3%)
Headache	9 (1.7%)	9 (1.7%)
Nausea	9 (1.7%)	10 (1.9%)
Hemorrhage NOS	8 (1.5%)	23 (4.4%)
Back Pain	8 (1.5%)	2 (0.4%)
Fever	8 (1.5%)	11 (2.1%)
Pain	8 (1.5%)	7 (1.3%)
Constipation	7 (1.3%)	9 (1.7%)
Rash	6 (1.2%)	8 (1.5%)
Dyspnea	6 (1.2%)	9 (1.7%)
Vomiting	5 (1.0%)	8 (1.5%)
Hematuria	5 (1.0%)	6 (1.1%)
Abdominal Pain	4 (0.8%)	6 (1.1%)
Diarrhea	3 (0.6%)	7 (1.3%)
Anemia	0	7 (1.3%)

NOS=not otherwise specified

[1] INNOHEP 175 IU/kg once daily SC. Unfractionated heparin initial IV bolus of 5,000 IU followed by continuous IV infusion adjusted to an aPTT of 1.5 to 2.5 or initial IV bolus of 50 IU/kg followed by continuous IV infusion adjusted to an aPTT of 2.0 to 3.0. In all groups treatment continued for approximately 6 to 8 days, and all patients received oral anticoagulant treatment commencing in the first 2 to 3 days.

Serious Adverse Events in Clinical Trials: Serious adverse events reported at a frequency ≥1% in 4,000 patients who received INNOHEP in clinical trials are provided in Table 3.

Table 3. Serious Adverse Events Associated With INNOHEP in Clinical Trials

Category	Serious Adverse Event
Bleeding-related	Anorectal bleeding Cerebral/intracranial bleeding Epistaxis Gastrointestinal hemorrhage Hemarthrosis Hematemesis Hematuria Hemopericardium Hemorrhage (not otherwise specified) Injection site bleeding Melena Purpura Retroperitoneal/intra-abdominal bleeding Vaginal hemorrhage Wound hematoma
Organ dysfunction	Angina pectoris Cardiac arrhythmia Dependent edema Myocardial infarction/coronary thrombosis Thromboembolism
Fetal/neonatal	Congenital anomaly Fetal death Fetal distress
Cutaneous	Bullous eruption Erythematous rash Maculopapular rash Skin necrosis
Hematologic	Granulocytopenia Thrombocytopenia
Allergic reactions	Allergic reaction
Injection site reaction	Cellulitis
Neoplastic	Neoplasm

In a separate study of elderly patients aged 70 years or over with renal impairment, there was a higher mortality rate observed in patients treated with INNOHEP (11.5%) than in those treated with UFH (6.3%). All of the deaths in the INNOHEP group were assessed as "not related to study drug" by the investigators (see Human Studies, IRIS).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and Lymphatic System Disorders: Thrombocytopenia (type 1) has been observed with INNOHEP use.

Hepatobiliary Disorders: A significant but transient increase of the liver transaminases (AST and ALT) has been observed with INNOHEP. This is a consistent finding with all members of the LMWH class, as well as with unfractionated heparin. However, no consistent irreversible liver damage has been observed. Normalization of transaminase levels can be expected within 2 to 4 weeks of the last dose of INNOHEP. The mechanism associated with the increased levels of liver transaminases has not been elucidated.

Transaminase increases occurred after more than three days of INNOHEP treatment in clinical studies. The increase is dose-dependent and has been observed at doses as low as 50 anti-Xa IU/kg once daily. In one study, at a dose of 150 anti-Xa IU/kg twice daily, all subjects showed increased plasma levels of AST and ALT from a mean of 17.8 to 128.5 U/L and 19.3 to 257.0 U/L respectively. These elevations correspond to a seven to twelve-fold increase as compared to the post-study evaluation performed within seven days of study completion.

Rarely, increases in gamma-GT, LDH and lipase have been observed. These increases are reversible after drug withdrawal.

Immune System Disorders: Allergic reactions of all types and severities are uncommon but have been reported.

Skin and Subcutaneous Tissue Disorders: There have been infrequent reports of various types of skin rash (such as erythematous and maculopapular), pruritus and urticaria. In rare instances, skin necrosis has been observed.

Post-Market Adverse Drug Reactions

Blood and Lymphatic System Disorders: In some cases, severe immunologically-mediated heparin-induced thrombocytopenia (type II) has been seen resulting in arterial and/or venous thrombosis or thromboembolism (see WARNINGS AND PRECAUTIONS, Hematologic). The incidence is rare, occurring in < 0.1%. An increase in platelet count which is asymptomatic and reversible has been observed.

Immune System Disorders: Allergic reactions of all types and severities have been reported. Hypersensitivity reactions, including angioedema and anaphylactoid reactions, have been observed rarely with unfractionated heparin and LMWHs. INNOHEP should be discontinued in patients showing local or systemic allergic responses.

Metabolism and Nutrition Disorders: Hypoaldosteronism associated with hyperkalaemia and metabolic acidosis has been reported with LMWHs especially in patients with renal impairment and diabetes mellitus.

Musculoskeletal and Connective Tissue Disorders: Use of LMWH over extended periods has been reported to be associated with development of osteopenia / osteoporosis. The frequency of occurrence with INNOHEP is not known.

Reproductive System and Breast Disorders: Occurrences of priapism have been reported.

Skin and Subcutaneous Tissue Disorders: There have been isolated reports of toxic epidermal necrolysis and Stevens-Johnson syndrome.

DRUG INTERACTIONS

INNOHEP (tinzaparin sodium) should be used with caution in patients receiving oral anticoagulants, NSAIDs, platelet inhibitors and thrombolytic agents because of increased risk of bleeding.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Use in Patients with Renal Impairment: All patients with renal impairment treated with LMWHs should be monitored carefully.

Administration of LMWHs to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance < 30 mL/min), leading to increased risk of bleeding. The effect of renal impairment on tinzaparin anti-Xa activity has not been fully studied. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

Administration

INNOHEP (tinzaparin sodium) is administered by subcutaneous injection, or systemically in the setting of hemodialysis. It must NOT be administered by intramuscular injection (see WARNINGS AND PRECAUTIONS, General).

Recommended Dose and Dosage Adjustment

I. Prevention of Postoperative Venous Thromboembolism in Orthopaedic Surgery

Hip Surgery: INNOHEP 50 anti-Xa IU/kg given by subcutaneous injection two hours before surgery followed by 50 anti-Xa IU/kg once daily for 7-10 days.

or

INNOHEP 75 anti-Xa IU/kg given post-operatively by subcutaneous injection once daily for 7-10 days.

Knee Surgery: INNOHEP 75 anti-Xa IU/kg given post-operatively by subcutaneous injection once daily for 7-10 days.

For convenience, the following prefilled syringes are available for dosing by body weight:

Dose per syringe	Pre-operative 50 anti-Xa IU/kg Body weight*	Post-operative 75 anti-Xa IU/kg Body weight*
2,500 anti-Xa IU	—	—
3,500 anti-Xa IU	70 (60 – 80) kg	45 (35 – 55) kg
4,500 anti-Xa IU	90 (80 – 100) kg	60 (50 – 70) kg

*Value represents the average weight ±10 kg appropriate for the syringe size. Patients outside of these weight ranges should be dosed on an individual basis

II. Prevention of Postoperative Venous Thromboembolism in General Surgery
INNOHEP 3500 anti-Xa IU (available in a prefilled syringe) given by subcutaneous injection two hours before surgery followed by 3500 anti-Xa IU once daily for 7-10 days.

III. Treatment of Deep Vein Thrombosis, with or without Pulmonary Embolism or, Treatment of Pulmonary Embolism
The recommended dosage is 175 anti-Xa IU/kg body weight given subcutaneously once daily at the same time every day. Although trials for DVT treatment did not include a maximum daily dose, few patients were included who exceeded 105 kg. Therefore, the recommended maximum daily dose for INNOHEP is 18,000 anti-Xa IU/day. In clinical trials, plasma anti-Xa levels were typically in the range of <0.3 anti-Xa IU/mL before injection and < 1.8 anti-Xa IU/mL approximately 5 hours after injection (dosed by body weight) as determined by a functional anti-Xa assay.

Concomitant treatment with oral anticoagulants (vitamin K antagonists) is usually started immediately. Treatment with INNOHEP should be continued until therapeutic oral anticoagulant effect has been achieved (INR 2.0 to 3.0), usually within 5 days. The average duration of INNOHEP administration is 7 days.

Published clinical data are available documenting extended treatment with INNOHEP 175 IU/kg once daily for 3-6 months in patients with cancer associated thrombosis (see, REFERENCES 6-8, 14). The use of INNOHEP beyond 6 months must be evaluated in the absence of clinical data.

For convenience, the following prefilled graduated syringes are available for dosing by body weight (175 anti-Xa IU/kg):

Patient Body Weight (Kg)	**DVT Treatment 175 anti-Xa IU/kg SC Once Daily 20,000 IU/mL**	
	Dose (IU)	**Amount (mL)**
31 - 36	6,000	0.3
37 - 42	7,000	0.35
43 - 48	**8,000**	**0.4**
49 - 53	9,000	0.45
54 - 59	**10,000**	**0.5**
60 - 65	11,000	0.55
66 - 70	**12,000**	**0.6**
71 - 76	13,000	0.65
77 - 82	**14,000**	**0.7**
83 - 88	15,000	0.75
89 - 93	**16,000**	**0.8**
94 - 99	17,000	0.85
100 - 105	**18,000**	**0.9**

IV. Anticoagulation of Extracorporeal Circulation and Haemodialysis

All patients participating in clinical trials were stable, chronic renal failure patients. The following dosage recommendations are for that patient population; in patients with lower risk of haemorrhage.

Optimisation of dosage is required for each individual patient (different clotting stimuli are produced by different dialysis circuits and membranes, and there is inter-patient variability).

The recommended starting dose is INNOHEP 4,500 anti-Xa IU administered as a bolus dose into the arterial side of the dialyser (or intravenously) at the beginning of the dialysis for a session lasting 4 hours or less in patients with no risk of haemorrhage. This dose normally produces plasma anti-Xa levels in the range of 0.5-1.0 IU anti-Xa/mL. Dosage modifications should

consider the outcome of the previous dialysis and should be made by increasing or decreasing the dose in steps of 500 anti-Xa IU until a satisfactory dose is obtained.

A larger starting dose may be given for dialysis sessions lasting longer than 4 hours. Doses in subsequent dialysis sessions should be adjusted as required.

In patients with a risk of haemorrhage, dialysis sessions may be carried out using halved doses. An additional smaller dose may be given during dialysis for sessions lasting longer than 4 hours. The dose in subsequent dialysis sessions should be adjusted as necessary to achieve plasma levels within the range of 0.2-0.4 IU anti-Xa/mL.

No anticoagulant should be added to the dialyser circuit when using this regimen.

OVERDOSAGE

Accidental overdosage following administration of INNOHEP (tinzaparin sodium) may lead to haemorrhagic complications. INNOHEP should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of INNOHEP is inhibited by protamine. This effect may be largely neutralised by slow intravenous injection of protamine sulphate. Each mg of protamine sulphate neutralises approximately 100 anti-Xa IU of tinzaparin sodium. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of INNOHEP may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-factor Xa activity is never completely neutralised (maximum about 60-65%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

INNOHEP (tinzaparin sodium) is a LMWH, produced by enzymatic depolymerization of unfractionated heparin from porcine intestinal mucosa. It is a heterogeneous mixture of sulphated polysaccharide glycosaminoglycan chains. The mass-average molecular weight mass ranges between 5500 and 7500 daltons. The mass percentage of chains lower than 2000 daltons is not more than 10 percent. The mass percentage of chains between 2000 and 8000 daltons ranges between 60 and 72 percent. The mass percentage of chains above 8000 daltons ranges between 22 and 36 percent. Tinzaparin sodium is composed of molecules with and without a specially characterized pentasaccharide, which is the specific site for high affinity binding to the plasma protein antithrombin III (AT III). This binding to AT III leads to an accelerated inhibition of factor Xa. This results in the antithrombotic effect of tinzaparin, although other mechanisms may also be involved since it potentiates the inhibition of several activated coagulation factors.

INNOHEP is an antithrombotic agent with higher anti-Xa activity (70-120 IU/mg) than anti-IIa activity (approximately 55 IU/mg). The ratio of anti-Xa to anti-IIa activity for INNOHEP is 2.0 ± 0.5, whereas it is 1 for unfractionated heparin.

Pharmacodynamics

Neither INNOHEP nor heparin doses can be measured directly in the bloodstream. Their effects on clotting are a function of the dose. Unfractionated heparin is usually measured by prolongation of APTT, although plasma anti-Xa can also be determined. INNOHEP only causes APTT prolongation at higher doses. In the therapeutic range, the effects of INNOHEP on the plasma anti-Xa activity can be measured as an indication of serum tinzaparin levels. However, clinical trials have not demonstrated a linear correlation between anti-Xa activity and antithrombotic effect. Prophylactic doses of 75 IU/kg of INNOHEP by subcutaneous administration resulted in peak anti-Xa activity of 0.31 to 0.42 IU/mL in patients whereas the mean ratio of peak APTT (as compared to baseline) was 1.13 to 1.35. Treatment doses of 175 anti-Xa IU/kg resulted in peak anti-Xa activity of approximately 0.4 to 1.8 IU/mL and a mean peak APTT ratio of 1.71 to 2.63. APTT values associated with either the prophylaxis or

treatment dose of INNOHEP returned to baseline within 20-28 hours after administration. APTT values associated with LMWHs are variable and are not predictive of clinical efficacy or safety.

Pharmacokinetics

Absorption and Distribution: The bioavailability of INNOHEP following subcutaneous injection is about 90% in healthy subjects when measured as anti-Xa activity versus 67% for anti-IIa activity. The absorption half-life of anti-Xa activity is 200 minutes and that of anti-IIa activity is 257 minutes. The long duration of action of tinzaparin is a result of its prolonged absorption.

Peak plasma anti-Xa activity occurs at approximately 4-6 hours. Detectable anti-Xa activity persists for 24 hours after injection, despite elimination half lives of anti-Xa activity of 82 minutes and anti-IIa of 71 minutes. No evidence of accumulation was found when INNOHEP was administered once daily for five days at a dose of 175 anti-Xa IU/kg. The volume of distribution of anti-Xa activity is 4 L and that of anti-IIa activity is 10.9 L. Possibly this higher value may occur because of higher protein binding of anti-IIa fractions, particularly to platelet factor 4.

The effect of tinzaparin on APTT values is inconsistent and generally only shows a dose-dependent effect at doses above 5000 anti-Xa IU.

Metabolism and Excretion: The primary route of tinzaparin elimination is by the kidney; hepatic elimination is not involved. Unlike unfractionated heparin, tinzaparin does not undergo metabolism to smaller molecules as a result of binding to endothelial cells.

Special Populations and Conditions

Renal Insufficiency: The half-life for anti-Xa activity for LMWHs is prolonged in patients with impaired renal function relative to people with normal function. The effect of renal impairment on tinzaparin anti-Xa activity has not been fully studied (see WARNINGS, PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Use in Patients with Renal Impairment).

STORAGE AND STABILITY

INNOHEP (tinzaparin sodium) should be stored at room temperature (15 to 25 ^{o}C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

INNOHEP contains tinzaparin sodium in a sterile solution for subcutaneous injection, available in unit-dose safety syringes, unit-dose graduated safety syringes and multi-dose 2 mL vials. Pre-filled syringes have a 27-gauge, ½ inch needle. All INNOHEP syringes and vials are latex-free**.**

Composition

***Unit-dose Syringes* 10,000 anti-Xa IU/mL** (non-preserved):

Tinzaparin sodium (anti-Xa IU)	**Sodium acetate .3H_2O**	**Sodium hydroxide***	**Water for injection (to make final volume)**
2,500 IU/syringe	1.25 mg	q.s.	0.25 mL
3,500 IU/syringe	1.75 mg	q.s.	0.35 mL
4,500 IU/syringe	2.25 mg	q.s.	0.45 mL

*quantity sufficient for pH adjustment; pH range of the final solution is 5.0-7.5

***Unit-dose Graduated Syringes* 20,000 anti-Xa IU/mL** (non-preserved):

Tinzaparin sodium (anti-Xa IU)	**Sodium metabisulphite**	**Sodium hydroxide***	**Water for injection (to make final volume)**
8,000 IU/syringe	0.73 mg	q.s.	0.4 mL
10,000 IU/syringe	0.92 mg	q.s.	0.5 mL
12,000 IU/syringe	1.10 mg	q.s.	0.6 mL
14,000 IU/syringe	1.28 mg	q.s	0.7 mL
16,000 IU/syringe	1.46 mg	q.s.	0.8 mL
18,000 IU/syringe	1.65 mg	q.s	0.9 mL

*quantity sufficient for pH adjustment; pH range of the final solution is 5.0-7.5

Multi-dose Vials:

Tinzaparin Sodium (anti-Xa IU)	10,000 IU/mL†	20,000 IU/mL†
Sodium Metabisulphite	1.8 mg	3.1 mg
Benzyl Alcohol	10 mg	10 mg
Sodium Hydroxide	q.s.*	q.s.*
Water for injection to make	1.0 mL	1.0 mL
*quantity sufficient for pH adjustment; pH range of the final solution is 5.0-7.5 † provided in 2 mL vials as 20,000 IU/vial and 40,000 IU/vial respectively		

PART II : SCIENTIFIC INFORMATION

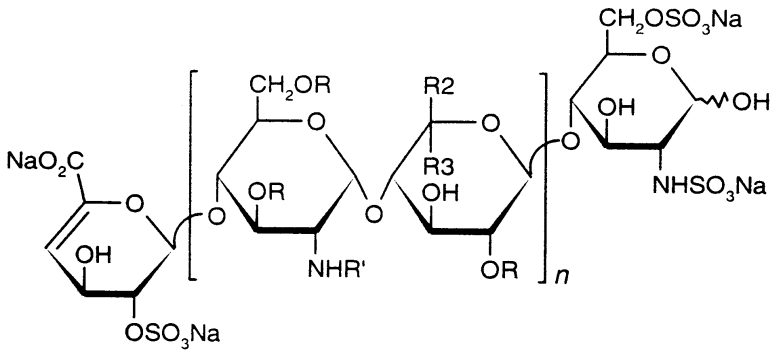
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tinzaparin Sodium

Chemical name: Polymers of alternating derivatives of D-glycosamine (N-sulphated or N-acetylated) and uronic acid (L-iduronic acid or D-glucuronic acid) joined by glycosidic linkages, the components being liberated in varying proportions on complete hydrolysis.

Structural formula:



n = 1 to 25 , R = H or SO_3Na , R' = H or SO_3Na or $COCH_3$

R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

Molecular mass: 4500 $\pm$ 1500 Daltons (Peak Maximum Molecular Mass)

Physicochemical properties: A white or yellowish powder, freely soluble in water, insoluble in organic solvents. pH of a 1% aqueous solution is between 5.5 and 8.0.

Origin: Porcine intestinal mucosa.

DETAILED PHARMACOLOGY

Animal Studies

The antithrombotic activity and anticoagulant activity of tinzaparin have been demonstrated in rats and rabbits in three different *in vivo* models and in rats and dogs in *ex vivo* model systems. These studies have shown that, as with unfractionated heparin, bleeding complications are the major side effect of tinzaparin. Tinzaparin is essentially devoid of significant secondary pharmacological effect. Tinzaparin had no effect on platelet aggregation *in vitro*. Although osteopenic effects of long-term treatment were not specifically determined, bone ash weights were lower in rats treated for 52 weeks with subcutaneous tinzaparin (25 mg/kg/day) or unfractionated heparin (12.5 mg/kg/day) compared to the vehicle control group.

Tinzaparin is well absorbed following subcutaneous administration. The bioavailability based on anti-Xa activity is 90%. The absorption half-life is over 3 hours. Dose-related increases in plasma anti-Xa and anti-IIa activity are observed with the peak activities of each seen 4 to 6 hours after administration. The anti-IIa activity is always less than the anti-Xa activity. The volume of distribution is approximately 4 L. Tinzaparin is not metabolized to any significant degree and is eliminated by a nonsaturable renal mechanism. The mean elimination half-lives of anti-Xa and anti-IIa activity are 82 minutes and 71 minutes, respectively.

Human Studies

The pharmacokinetic properties of tinzaparin are determined indirectly by plasma anti-Xa and anti-IIa activities. Following subcutaneous administration, dose related increases in peak activities have been observed 4 to 6 hours following subcutaneous administration. Anti-Xa activity is always greater than anti-IIa activity (see Table below). Both anti-Xa and anti-IIa plasma levels show correlation with body weight as well as with the administered dose.

Dose (anti-Xa IU)	Peak Plasma Anti-Xa Activity (Units/mL)	Peak Plasma Anti-IIa Activity (Units/mL)
2,500	0.12	0.02
5,000	0.28	0.03
10,000	0.54	0.08

Plasma levels of anti-thrombin III, platelet counts and the activated partial thromboplastin time (APTT) remain essentially unaltered following subcutaneous tinzaparin administration.

Anti-Xa levels have been reported to be undetectable in plasma 24 hours following low doses of 50 anti-Xa IU/kg in both single and repeat dose studies. At higher doses, 150 anti-Xa IU/kg once daily, plasma anti-Xa activity of 0.15 units/mL have been reported. However, no clinically relevant accumulation effect was found after repeated once daily subcutaneous administration of up to 175 anti-Xa IU/kg.

A correlation between the antithrombotic effect and anti-Xa activity was seen in animal experiments where the effect of different doses was determined shortly after administration of the drug. However, this does not correspond to the increasing/decreasing plasma concentrations during 24 hours after subcutaneous administration in patients. Peak serum anti-Xa levels are recommended for monitoring serum tinzaparin levels.

Pregnancy: In two studies tinzaparin was given SC and IV to healthy women undergoing therapeutic abortions by two different methods. Tinzaparin at a dose of 35 anti-Xa IU/kg or 40 anti-Xa IU/kg was compared with unfractionated heparin (70 anti-Xa IU/kg) and a placebo control group. The anti-Xa activity in the mother's plasma rose accordingly and no anti-Xa activity was found in the blood of the fetus. Heparin-like activity was measured in a competitive binding assay and could be demonstrated in all fetal groups including the controls.

There is no evidence of any transplacental passage of tinzaparin.

INNOHEP in Renal Insufficiency Study (IRIS): This was an international, multicentre, prospective, open, centrally randomised, parallel group study comparing treatment doses of INNOHEP (175 anti-Xa IU/kg once daily; N=269) and unfractionated heparin (UFH) (N=268) in the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in elderly patients. All patients were aged 70 years or older (INNOHEP mean age 82.9 years, range 73-101; UFH mean age 82.6 years, range 70-99) and had renal impairment (patients aged ≥75 years with a CrCl ≤60 ml/min; and patients aged ≥70 years with a CrCl ≤30 ml/min). Oral anticoagulants were co-administered with study drug on Days 1 to 3 and treatment continued for at least five days and until the international normalized ratio (INR) was between 2 to 3, on two consecutive days. Patients then continued on oral anticoagulants alone and were followed until

day 90 ± 5. Anti-Xa activity was assessed in a sub-set of IRIS patients under a prospective sub-study protocol. During a planned interim safety analysis, a difference in mortality was observed between the treatment groups and the study was stopped. The all cause mortality rates for patients at Day 90 ± 5 were 6.3% (17/268) in the UFH group and 11.5% (31/269) in the INNOHEP group. There was no clear explanation for this difference; however mortality was not due to recurrent VTE or bleeding. Since the study was stopped prematurely, no definitive conclusions could be drawn from this study.

Published Clinical Trials in Patients with Cancer:

Information for INNOHEP in support of extended treatment for patients with cancer comes from the published clinical trials of Hull (LITE) and Romera (see REFERENCES 6-8, 14). In these clinical trials, INNOHEP has been studied in patients with cancer associated thrombosis at 175 IU/kg daily for 3 and 6 months respectively.

TOXICOLOGY

From the toxicological studies performed, it has been shown that the major risk of treatment with tinzaparin is loss of blood, either internal or external, due to bleeding.

Acute Toxicity

NMRI mice and Wistar rats were used in single dose toxicity studies involving tinzaparin and USP Heparin by intravenous and subcutaneous administration. The deaths seen in these studies, together with a few other signs seen in all the single dose studies, were caused by the exaggerated pharmacological effect of tinzaparin, namely massive loss of blood from the circulatory system caused by the effect of tinzaparin on the coagulation system. No other toxic effects of tinzaparin were seen even at extremely high dosages given once. The LD_{50} has not been established after either subcutaneous or intravenous administration.

Long-Term Toxicity

Repeated dose studies were performed in rats and dogs; Two 4-week studies were performed by intravenous administration and two 52-week studies were performed by subcutaneous administration.

No signs of thrombocytopenia were seen in the repeated dose studies. In the one year dog study, only females showed increased plasma content of triglycerides, phospholipids and total

cholesterol. Heparin and LMWH activate lipoprotein lipase and hepatic lipase, enhance plasma lipolytic activity and elevate plasma levels of free fatty acid in man. It is believed the effect seen in the female dogs may reflect these characteristics.

From the repeated dose studies, an increased spleen weight was found in connection with extra-medullar haematopoiesis. Further, increased liver and kidney weights were observed but no histopathological changes were found in these organs. It has been postulated that increased liver weight may be due to this organ containing the first binding sites of tinzaparin to the reticuloendothelial system. The kidneys are the main excreting organ for heparin and heparin-like substances and the increased kidney weight is thought to be an adaptive reaction to treatment.

From the repeated dose studies carried out in rats and dogs, it can be concluded that tinzaparin was well tolerated.

Mutagenicity

In four mutagenicity tests tinzaparin showed no evidence of chromosomal damage or mutagenic potential.

Carcinogenicity

An investigation into former use of heparin in humans or into research data from animal studies did not indicate any oncogenic or carcinogenic potential nor did the production of tinzaparin introduce any elements which should be taken into consideration. Furthermore, none of the above mentioned toxicological studies on tinzaparin indicate any carcinogenic risks. As a result, no animal carcinogenicity studies have been performed.

Reproduction and Teratology

The reproduction studies showed that tinzaparin had no effect on fertility in male and female rats or on their F_1 generation progeny. Fetal development and teratogenicity studies produced no evidence of embryotoxic or teratogenic effects in rats and rabbits. Peri- and post-natal development studies indicated that tinzaparin had no toxic effects on the F_1 or F_2 generation.

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PART III : CONSUMER INFORMATION
[Pr]innohep®
(tinzaparin sodium)

This leaflet is part III of a three-part "Product Monograph" published when innohep® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about innohep®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- to prevent blood clots forming in patients having orthopaedic or general surgery
- to treat blood clots and their complications
- to prevent bloods clots forming in dialysis lines

What it does:
Innohep® works to prevent blood clots from forming or getting any bigger.

When it should not be used:
Do not use innohep® if you have or have had any of the following:
- an allergy to innohep® or its ingredients (e.g. benzyl alcohol, sodium metabisulphite) or to other LMWHs and/or heparin
- a history of decreased platelet count
- a bacterial infection of the heart
- bleed easily or have conditions or diseases with a high risk of bleeding
- a blood clotting disorder which increases your risk of bleeding
- a cerebrovascular accident (e.g. stroke)
- a stomach or intestinal ulcer or an ulcerating cancer
- uncontrolled, severe high blood pressure
- eye disorders due to diabetes or bleeding
- an injury or surgery on the brain, spinal cord, eyes or ears
- an artificial heart valve
- a spinal/epidural anaesthesia and need high doses of innohep® as this increases the risk of bleeding

The multi-dose vials of innohep® contain benzyl alcohol and must not be given to children < 2yrs, premature infants or newborns due to the risk of developing gasping syndrome

What the medicinal ingredient is:
Tinzaparin sodium (a low molecular weight heparin)

What the important non-medicinal ingredients are:
The graduated syringes contain sodium metabisulphite. The multi-dose vials contain benzyl alcohol and sodium metabisulphite.

What dosage forms it comes in:
Pre-filled single-use safety syringes:

10,000 anti-Xa IU /mL		
2,500 IU/0.25 mL	3,500 IU/0.35 mL	4,500 IU/0.45 mL

20,000 anti-Xa IU/mL		
8,000 IU/0.4 mL	12,000 IU/0.6 mL	16,000 IU/0.8 mL
10,000 IU/0.5 mL	14,000 IU/0.7 mL	18,000 IU/0.9 mL

Multi-dose vials: 20,000 IU/2mL and 40,000 IU/2mL

Syringes have a 27-gauge, ½ inch needle. All innohep® syringes and vials are latex-free.

WARNINGS AND PRECAUTIONS

- innohep® should not be given by intramuscular injection.
- Do not take other medications by intramuscular injection while you are taking innohep®.
- Benzyl alcohol may cross the placenta, therefore innohep® multi-dose vials should not be used in pregnant women.
- The sodium metabisulphite in innohep® can cause severe allergic reaction in asthmatics or those with sulphite sensitivity.
- innohep® should be used with caution in patients with poor renal function and is not recommended in those aged >70yrs with kidney disease.
- innohep® should be used with caution in patients taking oral anticoagulants

BEFORE you use innohep® talk to your doctor or pharmacist if you:
- have liver or kidney disease. Elderly patients should have their kidney function checked by the doctor.
- have stomach or intestinal ulcers or have diabetes
- are asthmatic or have a sensitivity to sulphites
- bleed easily, have a medical condition with a risk of bleeding or have low platelet levels
- have high blood pressure or had a stroke
- are pregnant, nursing or planning on becoming pregnant
- have a prosthetic heart valve
- if you need to consult with another doctor or see your dentist, be absolutely sure to tell them that you are being treated with innohep®

INTERACTIONS WITH THIS MEDICATION

Innohep® should be used with caution in patients taking oral anticoagulants, NSAIDS, platelet inhibitors and thrombolytic agents.

Tell your doctor about all the drugs you are taking, including non prescription medicines. Do not take any drugs other than those prescribed by your doctor while you are taking innohep®.

PROPER USE OF THIS MEDICATION

Innohep® should be injected just under the surface of the skin i.e. subcutaneously (with the exception of dialysis).

Hip and Knee Surgery: A subcutaneous injection is given after surgery, once a day for 7 to 10 days. You may also receive an injection 2 hours before surgery.
General Surgery: A subcutaneous injection is given 2 hours before surgery followed by an injection once daily after surgery for 7 to 10 days.
To Treat Blood Clots: A treatment (175 anti-Xa IU/kg) dose is given once daily usually for 5 to 7 days. In some cases, longer treatment is needed. Treatment may last for 3 to 6 months. Follow the treatment period prescribed by your doctor. At the same time, you may be given a blood thinner (pill). Take both medicines as instructed.

For Hemodialysis: A single dose is delivered into the dialyser tubing at the beginning of a dialysis session. Doses in subsequent dialysis sessions are adjusted as necessary. If you are at risk for bleeding, dialysis is done using halved doses.

At home: Follow the instructions of your doctor or nurse carefully. Only take the prescribed dose of innohep® for the time period specified by your doctor.

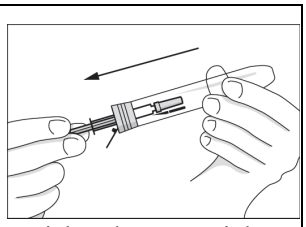
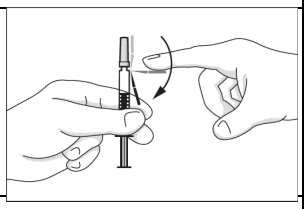
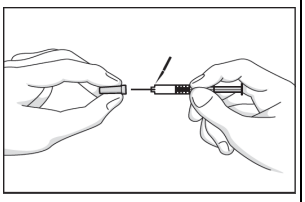
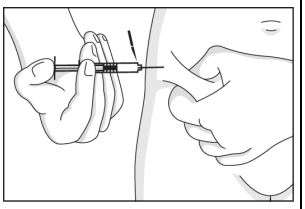
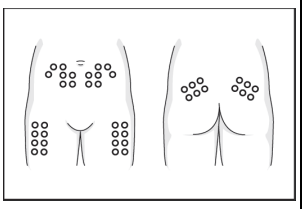
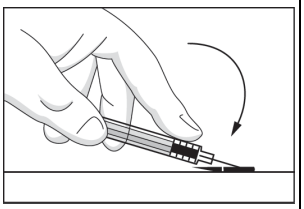
Preparing the Dose (use clean hands):
Graduated syringes: Before using this syringe, you may need to adjust the volume to the amount prescribed by your doctor. To adjust the dose, hold the syringe with the needle pointing up and gently tap the syringe to move the air bubble to the top of the syringe. Remove the cap. Slowly push the syringe plunger up to push the air bubble out. Continue to slowly push the plunger up until the edge of the rubber stopper reaches the line matching your dose. Follow "self-injection" instructions below.

If you don't need to adjust the dose, it is not necessary to remove the air bubble in the syringe before injecting. Follow the "self-injection" instructions below.

Multi-dose vials: Using a 1 mL syringe with a 25-27 gauge, 1/2 inch needle, insert the needle into the vial. Turn the vial upside down and pull back slowly on the plunger to draw up the desired dose. Draw up more if you see an air bubble in the syringe. Tap the syringe lightly and carefully remove air bubbles with a gentle push on the plunger. Check that you have the correct dose. If necessary, re-cap needle until ready for use.

Instructions for Self-injection:
A proper injection technique will help prevent pain and bruising at the injection site. Innohep® safety syringes are designed to prevent needle stick injuries. Follow these instructions carefully for proper use of the safety device.

Wash your hands before you inject the medicine. Gently wipe (do not rub) the skin around the injection site clean using an alcohol swab and let skin dry.

1.	Open the storage tube by flipping the tab back and bending the coloured lid all the way back. Remove the syringe and inspect the content of the syringe before you use it.  If the medicine is cloudy or has particles, do not use it but take another syringe. A clear to slightly yellow solution is fine to use.
2.	Before removing needle cap, bend the safety device (orange tab) down and away from the cap on the needle. 
3.	Pull the protective needle cap straight off without bending the needle. If necessary, adjust the syringe to the dose prescribed by your doctor as previously described. 
4.	Hold a fold of skin gently between your thumb and index finger. With the other hand gently insert the needle straight (at a right angle) into the skin fold. Be careful not to inject into the muscle. Ensure the safety device is not in the way 
5.	Push the plunger all the way down and slowly inject the dose into the fatty tissue of the skin. The preferred location is to inject your lower stomach. You can also inject the sides of the thigh, the lower back or the upper arm. Avoid the belly button area.  Wait a few seconds for the solution to spread out. Gently remove the needle and then release the skin fold. Using a cotton swab, apply light pressure at the injection site. Choose a different injection site next time (for e.g., move from the left to the right side of the stomach).
6.	Using the edge of a hard surface bring the safety device up from underneath back to its original position against the needle. Place the safety device flat against a hard surface and press down firmly on the syringe until the needle locks «clicks» into the device. 

7.	Place the used syringe in the storage tube with the needle facing down and cap the tube or discard the syringe in a sharps container. The syringe is now safely secured. Take the tube or sharps container to the hospital or your pharmacist for disposal. Keep used syringe away from children.

Missed dose:
If you miss a dose, do not double up. Continue with your next injection as scheduled. If you are not sure what to do, talk to your doctor or pharmacist.

Overdose:
Accidental overdose may result in bleeding which can not be treated at home.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Administration of innohep® may result in bleeding which can have serious or life-threatening consequences. Strokes and serious internal bleeding have been reported. Innohep® is generally well tolerated when used according to directions for use.

If you notice any of the following effects while you are being treated with innohep®, contact your doctor promptly:
- bleeding at the injection site and/or from surgical sites
- easy bruising or bruising without apparent cause
- allergic reactions
- other bleeding such as nose bleeds, blood in the urine, coughing or throwing up blood, or bleeding gums while brushing teeth
- purplish or reddish discolouration or pain and bruising around the injection site

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Stop taking drug and call your doctor or pharmacist
Rare: Major bleeding events (e.g. at a surgical site, stroke, blood in the urine.)	√
Rare: Allergic reaction (incl. severe asthmatic episode)	√

This is not a complete list of side effects. For any unexpected effects while taking innohep®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature between 15 to 25 °C. Keep innohep® in a safe place out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  Fax toll-free to 1-866-678-6789, or
  Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.leo-pharma.com\canada
or by contacting the sponsor, LEO Pharma Inc. at: 1-800-668-7234

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