

## ATTACHMENT

DRAFT

6536-00/July 2000

**Innohep®**  
(tinzaparin sodium injection)

R<sub>x</sub> only

For Subcutaneous Use Only

### **SPINAL/EPIDURAL HEMATOMAS**

**When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.**

**The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.**

**Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.**

**The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage, and PRECAUTIONS, Drug Interactions).**

### **DESCRIPTION**

INNOHEP is a sterile solution, containing tinzaparin sodium, a low molecular weight heparin. It is available in a multiple dose 2 mL vial.

Each 2 mL vial contains 20,000 anti-Factor Xa IU (anti-Xa) of tinzaparin sodium per mL, for a total of 40,000 IU, and 3.1 mg/mL sodium metabisulfite as a stabilizer. The vial contains 10 mg/mL benzyl alcohol as a preservative. Sodium hydroxide may be added to achieve a pH range of 5.0 to 7.5.

**Table 1. Composition of 20,000 anti-Xa IU/mL  
INNOHEP (tinzaparin sodium injection)**

Component	Quantity per mL
Tinzaparin sodium	20,000 anti-Xa IU
Benzyl alcohol, USP	10 mg
Sodium metabisulfite, USP	3.106 mg <sup>1</sup>
Sodium hydroxide, USP	as necessary
Water for Injection, USP	q.s. to 1 mL

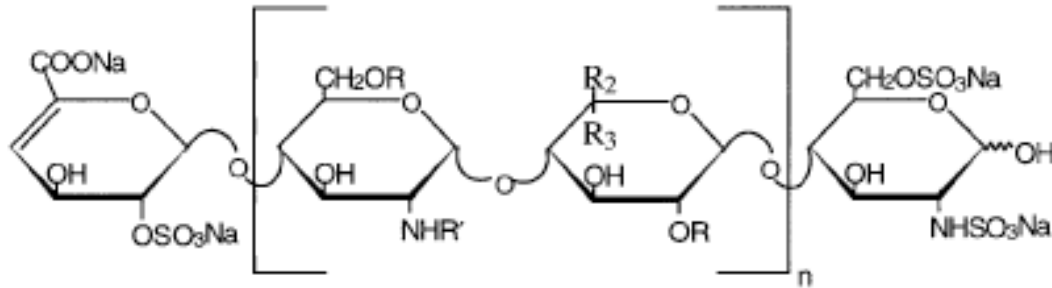
<sup>1</sup>Corresponding to 3.4 mg/mL sodium bisulfite

Tinzaparin sodium is the sodium salt of a low molecular weight heparin obtained by controlled enzymatic depolymerization of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. The majority of the components have a 2-O-sulpho-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulpho-D-glucosamine structure at the reducing end of the chain.

Potency is determined by means of a biological assay and interpreted by the first International Low Molecular Weight Heparin Standard as units of anti-factor Xa (anti-Xa) activity per milligram. The mean tinzaparin sodium anti-factor Xa activity is approximately 100 IU per milligram. The average molecular weight ranges between 5,500 and 7,500 daltons. The molecular weight distribution is:

<2,000	Daltons	<10%
2,000 to 8,000	Daltons	60% to 72%
>8,000	Daltons	22% to 36%

**Structural Formula:**



$n = 1$  to  $25$ ,  $R = H$  or  $SO_3Na$ ,  $R' = H$  or  $SO_3Na$  or  $COCH_3$   
 $R_2 = H$  and  $R_3 = COONa$  or  $R_2 = COONa$  and  $R_3 = H$

**CLINICAL PHARMACOLOGY**

Tinzaparin sodium is a low molecular weight heparin with antithrombotic properties. Tinzaparin sodium inhibits reactions that lead to the clotting of blood including the formation of fibrin clots, both *in vitro* and *in vivo*. It acts as a potent co-inhibitor of several activated coagulation factors, especially factors Xa and IIa (thrombin). The primary inhibitory activity is mediated through the plasma protease inhibitor, antithrombin.

Bleeding time is usually unaffected by tinzaparin sodium. Activated partial thromboplastin time (aPTT) is prolonged by therapeutic doses of tinzaparin sodium used in the treatment of deep vein thrombosis (DVT). Prothrombin time (PT) may be slightly prolonged with tinzaparin sodium treatment but usually remains within the normal range. Neither aPTT nor PT can be used for therapeutic monitoring of tinzaparin sodium.

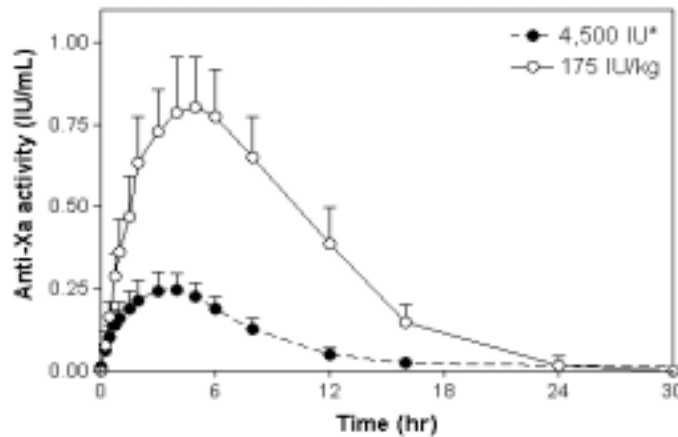
Neither unfractionated heparin nor tinzaparin sodium have intrinsic fibrinolytic activity; therefore, they do not lyse existing clots. Tinzaparin sodium induces release of tissue factor pathway inhibitor, which may contribute to the antithrombotic effect. Heparin is also known to have a variety of actions that are independent of its anticoagulant effects. These include interactions with endothelial cell growth factors, inhibition of smooth muscle cell proliferation, activation of lipoprotein lipase, suppression of aldosterone secretion, and induction of platelet aggregation.

**Pharmacokinetics/Pharmacodynamics**

Anti-Xa and anti-IIa activities are the primary biomarkers for assessing tinzaparin sodium exposure because plasma concentrations of low molecular weight heparins cannot be measured directly. Because of analytical assay limitations, anti-Xa activity is the more widely used biomarker. 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 (anti-Xa and anti-IIa activities). Monitoring patients based on anti-Xa activity is generally not advised. The data are provided in Figure 1 and Table 2 below.

Studies with tinzaparin sodium in healthy volunteers and patients have been conducted with both fixed- and weight-adjusted dose administration. Recommended therapy with tinzaparin sodium is based on weight-adjusted dosing (see **DOSAGE AND ADMINISTRATION**).

**Figure 1. Mean and Standard Deviation of Anti-Xa Activity Following a Single SC Administration of 175 IU/kg and 4,500 IU\* Tinzaparin Sodium to Healthy Volunteers**



\*Dosing based on fixed dose of 4,500 IU. Mean dose administered was 64.3 IU/kg.

**Table 2. Summary of Pharmacokinetic Parameters (Mean and Standard Deviation) Based on Anti-Xa Activity Following a Single SC Administration of Tinzaparin Sodium to Healthy Volunteers**

Parameter	Dose	
	4,500 IU*	175 IU/kg
Cmax (IU/mL)	0.25 (0.05)	0.87 (0.24)
Tmax (hr)	3.7 (0.9)	4.7 (1.1)
AUC <sub>0-∞</sub> (IU*hr/mL)	2.0 (0.5)	9.6 (1.6)
Half-life (hr)	3.4 (1.7)	3.9 (0.9)

\*Dosing based on fixed dose of 4,500 IU. Mean dose administered was 64.3 IU/kg.

**Absorption**

Plasma levels of anti-Xa activity increase in the first 2 to 3 hours following SC injection of tinzaparin sodium and reach a maximum within 4 to 5 hours. Maximum concentrations (Cmax) of 0.25 and 0.87 IU/mL are achieved following a single SC fixed dose of 4,500 IU (approximately 64.3 IU/kg) and weight-adjusted dose of 175 IU/kg of tinzaparin sodium, respectively. Following a single SC injection of tinzaparin sodium, the mean anti-Xa to anti-IIa activity ratio, based on the area under the anti-Xa and anti-IIa time profiles, is 2.8 and is higher than that of unfractionated heparin (approximately 1.2). The absolute bioavailability (following

4,500 IU SC and intravenous [IV] administrations) is 86.7% based on anti-Xa activity. Based on the extent of absorption ( $AUC_{0-\infty}$ ), a comparison of 4,500 IU and 12,250 IU doses indicates that increases in anti-Xa activity are greater than dose proportional relative to the increase in dose.

### **Distribution**

The volume of distribution of tinzaparin sodium ranges from 3.1 L to 5.0 L. These values are similar in magnitude to blood volume, suggesting that the distribution of anti-Xa activity is limited to the central compartment.

### **Metabolism**

Low molecular weight heparins are partially metabolized by desulphation and depolymerization.

### **Elimination**

In healthy volunteers, the elimination half-life following SC administration of 4,500 IU or 175 IU/kg tinzaparin sodium is approximately 3-4 hours based on anti-Xa activity. Clearance following IV administration of 4,500 IU tinzaparin sodium is approximately 1.7 L/hr. The primary route of elimination is renal.

### ***Special Populations***

#### ***Population Pharmacokinetics***

Anti-Xa concentrations from approximately 180 patients receiving SC tinzaparin sodium once daily (175 IU/kg body weight) as the treatment of proximal DVT and approximately 240 patients undergoing elective hip replacement surgery receiving SC tinzaparin sodium once daily (~65 IU/kg body weight) were analyzed by population pharmacokinetic methods. The results indicate that neither age nor gender significantly alter tinzaparin sodium clearance based on anti-Xa activity (see **PRECAUTIONS, General**). However, a reduction in tinzaparin sodium clearance was observed in patients with impaired renal function (reduced calculated creatinine clearance). Weight is also an important factor for the prediction of tinzaparin sodium clearance, consistent with the recommendation that INNOHEP therapy be based on weight-adjusted dosing (see **DOSAGE AND ADMINISTRATION**).

#### **Renal Impairment**

In 6 patients undergoing hemodialysis for chronic renal failure, the half-life of anti-Xa activity following a single IV dose of 75 IU/kg of tinzaparin sodium was prolonged compared to that for healthy volunteers (5.2 versus 1.6 hours). In patients being treated with tinzaparin sodium (175 IU/kg) for DVT, a population pharmacokinetic (PK) analysis determined that tinzaparin sodium clearance based on anti-Xa activity was related to creatinine clearance calculated by the 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 24% reduction in tinzaparin sodium clearance relative

to the remainder of the patients in the study. Patients with severe renal impairment should be dosed with caution (see **PRECAUTIONS**).

### **Hepatic Impairment**

No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in hepatically impaired patients. However, the hepatic route is not a major route of elimination of low molecular weight heparins (see **WARNINGS, Hemorrhage**).

### **Elderly**

No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in healthy elderly volunteers. Since renal function is known to decline with age, elderly patients may show reduced elimination of tinzaparin sodium.

### **Obesity**

No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in obese subjects. Based on the results of the population PK analysis, dosing should be based on body weight; body weight adjusted exposure is sufficient to explain tinzaparin sodium clearance differences observed in patients of different body mass index (BMI). Clinical trial experience is limited in patients with a BMI >40 kg/m<sup>2</sup>.

## **CLINICAL STUDIES**

### Treatment of Acute Deep Vein Thrombosis (DVT) With or Without Pulmonary Embolism (PE)

In a randomized, multicenter, double-blind trial, INNOHEP was compared to unfractionated heparin in 435 hospitalized patients with symptomatic, proximal DVT. Six percent of the enrolled patients had symptomatic pulmonary embolism confirmed by segmental or greater lung scan defect. The study patients ranged in age from 19 to 92 years (mean 61 ± 17 years), 55% were male, 88% were white and 8% black. Patients received either INNOHEP SC once daily according to body weight (175 IU/kg) and a placebo IV bolus followed by continuous placebo IV infusion, or unfractionated heparin as an initial IV bolus dose (5,000 IU) followed by continuous IV infusion of unfractionated heparin with the rate adjusted according to the aPTT (1.5 to 2.5 times control value) and a once daily SC placebo injection. Treatment continued for approximately 6 days and both treatment groups also received oral warfarin sodium starting on Day 2 which continued to Day 90 with doses titrated to a target INR of 2.0 to 3.0.

The 90-day cumulative thromboembolic (TE) rate [recurrent DVT or PE] with INNOHEP was not significantly different than the rate with unfractionated heparin. The data are provided in Table 3.

**Table 3. Efficacy of Once Daily INNOHEP in the Treatment of Acute Deep Vein Thrombosis**

Indication	Dosing Regimen	
	INNOHEP <sup>1</sup> 175 IU/kg Once Daily SC  n (%)	Heparin <sup>1</sup> 5,000 IU Bolus then aPTT Adjusted Continuous Infusion IV n (%)
Treatment of Acute DVT		
Intent to Treat Population <sup>2</sup>	216 (100%)	219 (100%)
Patient Outcome at 90 days		
Total TE <sup>3</sup> Events	6 (2.8%) <sup>4</sup>	15 (6.8%) <sup>4</sup>
DVTs	3 (1.4%)	9 (4.1%)
PEs	3 (1.4%)	6 (2.7%)

<sup>1</sup> Patients were also treated with warfarin sodium commencing within 24-48 hours of tinzaparin sodium or standard heparin therapy

<sup>2</sup> All randomized patients who received at least one dose of active study drug

<sup>3</sup> TE = thromboembolic events (DVT and/or PE)

<sup>4</sup> The 95% Confidence Interval (CI) for the total TE event rate difference (4.0%) was 0.07%, 8.07%.

Mortality with INNOHEP was 4.6% (10 patients) and with heparin 9.6% (21 patients). The 95% confidence interval (CI) for the mortality difference was 0.16%, 9.76%.

In a multicenter, open-label, randomized clinical trial, INNOHEP was compared to unfractionated heparin as initial treatment for hospitalized patients with symptomatic PE not requiring thrombolytic therapy, embolectomy, or vena cava interruption. Patients were excluded if they carried an unusually high risk for thromboembolic and/or bleeding events or other complications. Of the 608 patients treated, 422 had documented DVT. Prior to determination of study eligibility and randomization, patients were allowed to receive unfractionated heparin; 78% of the patients received unfractionated heparin at therapeutic doses for up to 24 hours, and an additional 4% received heparin at therapeutic doses for greater than 24 hours. After randomization, INNOHEP was administered SC once daily, 175 IU/kg body weight; heparin as an initial IV bolus (50 IU/kg) followed by continuous IV infusion with the rate adjusted according to the aPTT (2-3 times control value). For both groups, treatment continued for approximately 8 days. All patients also received oral anticoagulant treatment starting in the first 3 days which continued to Day 90.

Thromboembolic events were infrequent for both treatment groups. No difference was observed between the two treatment groups for incidence of recurrence of thromboembolic events.

## **INDICATIONS AND USAGE**

INNOHEP is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of INNOHEP were established in hospitalized patients.

## **CONTRAINDICATIONS**

INNOHEP is contraindicated in patients with active major bleeding, in patients with (or history of) heparin-induced thrombocytopenia, or in patients with hypersensitivity to tinzaparin sodium.

Patients with known hypersensitivity to heparin, sulfites, benzyl alcohol, or pork products should not be treated with INNOHEP.

## **WARNINGS**

INNOHEP is not intended for intramuscular or intravenous administration.

INNOHEP cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medications has its own instructions for use.

**INNOHEP should not be used in patients with a history of heparin-induced thrombocytopenia (See CONTRAINDICATIONS).**

**Hemorrhage:** INNOHEP, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis; severe uncontrolled hypertension; congenital or acquired bleeding disorders including hepatic failure and amyloidosis; active ulcerative and angiodysplastic gastrointestinal disease; hemorrhagic stroke; shortly after brain, spinal or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. Bleeding can occur at any site during therapy with INNOHEP. An unexplained fall in hematocrit, hemoglobin, or blood pressure should lead to serious consideration of a hemorrhagic event. If severe hemorrhage occurs, INNOHEP should be discontinued.

**Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture which can result**



**in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or with the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and PRECAUTIONS, Drug Interactions).**

**Thrombocytopenia:** Thrombocytopenia can occur with the administration of INNOHEP.

In clinical studies, thrombocytopenia (platelet count  $<100,000/\text{mm}^3$  if baseline value  $\geq 150,000/\text{mm}^3$ ,  $\geq 50\%$  decline if baseline  $<150,000/\text{mm}^3$ ) was identified in 1% of patients given INNOHEP; severe thrombocytopenia (platelet count less than  $50,000/\text{mm}^3$ ) occurred in 0.13 %.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below  $100,000/\text{mm}^3$ , INNOHEP should be discontinued. Cases of thrombocytopenia with disseminated thrombosis have also been observed in clinical practice with heparins, and low molecular weight heparins, including tinzaparin sodium. Some of these cases were complicated by organ infarction or limb ischemia.

**Hypersensitivity:** INNOHEP contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown, but is probably low. Sulfite sensitivity is more frequent in asthmatic people than in non-asthmatic people.

**Priapism:** Priapism has been reported from post-marketing surveillance as a rare occurrence. In some cases surgical intervention was required.

**Miscellaneous:** INNOHEP multiple dose vial contains benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, INNOHEP preserved with benzyl alcohol should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS**, Pregnancy).

## **PRECAUTIONS**

**General:** INNOHEP should not be mixed with other injections or infusions.

INNOHEP should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension, or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

Consistent with expected age-related changes in renal function, elderly patients and patients with renal insufficiency may show reduced elimination of tinzaparin sodium. INNOHEP should be used with care in these patients (see **CLINICAL PHARMACOLOGY, Special Populations**).

**Laboratory Tests:** Periodic complete blood counts including platelet count and hematocrit or hemoglobin, and stool tests for occult blood are recommended during treatment with INNOHEP. When administered at the recommended doses, routine anticoagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are relatively insensitive measures of INNOHEP activity and, therefore, are unsuitable for monitoring.

**Drug Interactions:** Because of increased risk of bleeding, INNOHEP should be used with caution in patients receiving oral anticoagulants, platelet inhibitors (e.g., salicylates, dipyridamole, sulfinpyrazone, dextran, and NSAIDs including ketorolac tromethamine), and thrombolytics. If co-administration is essential, close clinical and laboratory monitoring of these patients is advised (see **PRECAUTIONS, Laboratory Tests**).

#### **Laboratory Test Interactions**

Elevation of Serum Transaminases: Asymptomatic reversible increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels have occurred in patients during treatment with INNOHEP (see **ADVERSE REACTIONS, Elevations of Serum Aminotransferases**). Similar increases in transaminase levels have also been observed in patients and volunteers treated with heparin and other low molecular weight heparins.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like INNOHEP should be interpreted with caution.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term studies in animals have been performed to evaluate the carcinogenic potential of tinzaparin sodium.

Tinzaparin sodium displayed no genotoxic potential in an *in vitro* bacterial cell mutation assay (AMES test), *in vitro* Chinese hamster ovary cell forward gene mutation test, *in vitro* human lymphocyte chromosomal aberration assay, and *in vivo* mouse micronucleus assay. Tinzaparin sodium at subcutaneous doses up to 1800 IU/kg/day in rats (about 2 times the maximum recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

#### **Pregnancy**

**Teratogenic Effects:** Pregnancy Category B: Teratogenicity studies have been performed in rats at subcutaneous doses up to 1800 IU/kg/day (about 2 times the maximum recommended human dose based on body surface area) and in rabbits at subcutaneous doses up to 1900 IU/kg/day (about 4 times the maximum recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to tinzaparin sodium. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during

pregnancy only if clearly needed.

There has been one case each reported of cleft palate, optic nerve hypoplasia, and trisomy 21 (Down's) syndrome in infants of women who received INNOHEP during pregnancy. A cause and effect relationship has not been established.

**Non-teratogenic Effects:** There have been four reports of fetal death/miscarriage in pregnant women receiving INNOHEP who had high risk pregnancies and/or a prior history of spontaneous abortion. Approximately 6% of pregnancies were complicated by fetal distress. There have been spontaneous reports of one case each of pulmonary hypoplasia or muscular hypotonia in infants of women receiving INNOHEP during pregnancy. A cause and effect relationship for the above observations has not been established.

Approximately 10% of pregnant women receiving INNOHEP experienced significant vaginal bleeding. A cause and effect relationship has not been established.

If INNOHEP is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazards to the fetus.

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 contains 20 mg of benzyl alcohol (10 mg of benzyl alcohol per mL) [see WARNINGS, Miscellaneous].

**Nursing Mothers:** In studies where tinzaparin sodium was administered subcutaneously to lactating rats, very low levels of tinzaparin sodium were found in breast milk. It is not known whether tinzaparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when INNOHEP is administered to nursing women.

**Pediatric Use:** Safety and effectiveness of tinzaparin sodium in pediatric patients have not been established.

**Geriatric Use:** In clinical studies for the treatment of DVT, 58% of patients were 65 or older and 29% were 75 and over. No significant overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity to tinzaparin sodium of some older individuals cannot be ruled out.

## **ADVERSE REACTIONS**

**Bleeding:** Bleeding is the most common adverse event associated with INNOHEP however, the incidence of major bleeding is low. In clinical trials, the definition of major bleeding included bleeding accompanied by  $\geq 2$  gram/dL decrease in hemoglobin, requiring transfusion of 2 or more

units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint. The data are provided in Table 4.

**Table 4. Major Bleeding Events<sup>1</sup> in Treatment of Acute Deep Vein Thrombosis With or Without Pulmonary Embolism**

Indication	Treatment Group <sup>1</sup>	
	INNOHEP  (N=519) %	Heparin  (N=524) %
Treatment of Acute DVT With or Without PE		
Major Bleeding Events <sup>2</sup>	0.8 <sup>3</sup>	2.7 <sup>3</sup>

<sup>1</sup> 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.

<sup>2</sup>Bleeding accompanied by  $\geq 2$  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.

<sup>3</sup>The 95% CI on the difference in major bleeding event rates (1.9%) was 0.33%, 3.47%.

**Thrombocytopenia:** In clinical studies thrombocytopenia was identified in 1% of patients treated with INNOHEP. Severe thrombocytopenia (platelet count  $< 50,000/\text{mm}^3$ ) occurred in 0.13% (see **WARNINGS, Thrombocytopenia**).

**Elevations of Serum Aminotransferases:** Asymptomatic increases in aspartate (AST [SGOT]) and/or alanine (ALT [SGPT]) aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in up to 8.8% and 13% for AST and ALT, respectively, of patients receiving tinzaparin sodium for the treatment of DVT. Similar increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are reversible and are rarely associated with increases in bilirubin (see **PRECAUTIONS, Laboratory Tests**).

**Local Reactions:** Mild local irritation, pain, hematoma, and ecchymosis may follow SC injection of INNOHEP. Injection site hematoma has been reported in approximately 16% of INNOHEP treated patients.

**Hypersensitivity:** Anaphylactic/anaphylactoid reactions may occur in association with INNOHEP use (see **CONTRAINDICATIONS** and **WARNINGS**).

**Adverse Events:** Adverse events with INNOHEP or heparin reported at a frequency of  $\geq 1\%$  in clinical trials with patients undergoing treatment for proximal DVT with or without PE, are provided in Table 5.

**Table 5. Adverse Events Occurring in  $\geq 1\%$  in Treatment of Acute Deep Vein Thrombosis With or Without Pulmonary Embolism Studies**

Adverse Event	Treatment Group <sup>1</sup>	
	INNOHEP (N=519) n (%)	Heparin (N=524) n (%)
Urinary Tract Infection	19 (3.7%)	18 (3.4%)
Pulmonary Embolism	12 (2.3%)	12 (2.3%)
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

<sup>1</sup>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.

**Other Adverse Events in Completed or Ongoing Trials:** Other adverse events reported at a frequency of  $\geq 1\%$  in 4,000 patients who received INNOHEP sodium in completed or on-going clinical trials are listed by body system:

*Body as a Whole:* injection site hematoma, reaction unclassified.

*Cardiovascular Disorders, General:* hypotension, hypertension.

*Central & Peripheral Nervous System Disorders:* dizziness.

*Gastro-Intestinal System Disorders:* flatulence, gastro-intestinal disorder (not otherwise specified), dyspepsia.

*Heart Rate and Rhythm Disorders:* tachycardia.

*Myo-, Endo-, Pericardial & Valve Disorders:* angina pectoris.

*Platelet, Bleeding & Clotting Disorders:* hematoma, thrombocytopenia.

*Psychiatric Disorders:* insomnia, confusion.

*Red Blood Cell Disorders:* anemia.

*Resistance Mechanism Disorders:* healing impaired, infection.

*Respiratory System Disorders:* pneumonia, respiratory disorder.

*Skin and Appendages Disorders:* rash erythematous, pruritus, bullous eruption, skin disorder.

*Urinary System Disorders:* urinary retention, dysuria.

*Vascular (Extracardiac) Disorders:* thrombophlebitis deep, thrombophlebitis leg deep.

Serious adverse events reported in clinical trials or from post-marketing experience are included in Tables 6 and 7 respectively:

**Table 6. Serious Adverse Events Associated with INNOHEP in Clinical Trials**

<b>Category</b>	<b>Serious Adverse Event</b>
Bleeding-related	Anorectal bleeding Cerebral/intracranial bleeding Epistaxis Gastrointestinal hemorrhage Hemarthrosis Hematemesis Hematuria Hemorrhage NOS 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 Skin necrosis
Hematologic	Granulocytopenia Thrombocytopenia
Allergic reactions	Allergic reaction
Injection site reaction	Cellulitis
Neoplastic	Neoplasm

**Table 7. Other Serious Adverse Events Associated with INNOHEP from Post-Marketing Surveillance**

<b>Category</b>	<b>Serious Adverse Event</b>
Organ dysfunction	Cholestatic hepatitis Increase in hepatic enzymes Peripheral ischemia Priapism
Bleeding-related	Hemoptysis Ocular hemorrhage Rectal bleeding
Cutaneous reactions	Epidermal necrolysis Ischemic necrosis Urticaria
Hematologic	Agranulocytosis Pancytopenia Thrombocytopenia
Injection site reactions	Abscess Necrosis
Allergic reactions	Angioedema
Fetal/Neonatal	Neonatal hypotonia
General	Acute febrile reaction

Ongoing Safety Surveillance: When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis (see boxed WARNING).

INNOHEP was first introduced in foreign markets in 1991. There have been no reports of spinal epidural hematoma in association with neuraxial anesthesia or spinal puncture with INNOHEP in clinical trials or in post-marketing surveillance.

There has been one case of spinal epidural hematoma with INNOHEP administered at a therapeutic dose in a patient who had not received neuraxial anesthesia or spinal puncture.

## **OVERDOSAGE**

**Symptoms/Treatment:** Accidental overdose of INNOHEP may lead to bleeding complications. Nosebleeds, blood in urine or tarry stools may be noted as the first signs of bleeding. Easy bruising or petechial hemorrhages may precede frank bleeding. In case of minor bleeding, the patient should be monitored for signs of more severe bleeding.

Of patients known to have received an overdose of tinzaparin sodium in clinical trials, defined as one or more doses >200 IU/kg for the treatment of DVT or >100 IU/kg for the prevention of DVT, approximately 16% experienced a bleeding complication.



Of spontaneous reports of probable overdosing with tinzaparin sodium, approximately 81% were accompanied by bleeding, usually hematoma. Most patients who have bleeding complications while receiving INNOHEP can be controlled by discontinuing INNOHEP, applying pressure to the site, if possible, and replacing volume and hemostatic blood elements (e.g., red blood cells, fresh frozen plasma, platelets) as required. In the event that this is ineffective, protamine sulfate can be administered.

In cases of serious bleeding or large overdose, protamine sulfate (1% solution) can be given by slow IV infusion at a dose of 1 mg protamine for every 100 anti-Xa IU of INNOHEP given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of INNOHEP may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. Even with the additional dose of protamine, the aPTT may remain more prolonged than would usually be found following administration of protamine to reverse unfractionated heparin. Protamine does not completely neutralize tinzaparin sodium anti-Xa activity (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions have been reported with protamine sulfate, it should be given only when resuscitation facilities are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.

Single subcutaneous doses of tinzaparin sodium at 22,000 and 7,700 IU/kg (about 10 and 7 times the maximum recommended human dose, respectively, based upon body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity included hematoma formation and bleeding at the injection site, anemia, decreased motor activity, unsteady gait, piloerection, and ptosis.

## **DOSAGE AND ADMINISTRATION**

All patients should be evaluated for bleeding disorders before administration of INNOHEP. Since coagulation parameters are unsuitable for monitoring INNOHEP activity, routine monitoring of coagulation parameters is not required (see **PRECAUTIONS, Laboratory Tests**).

### **Adult Dosage**

The recommended dose of INNOHEP for the treatment of DVT with or without PE is 175 anti-Xa IU/kg of body weight, administered SC once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin (INR at least 2.0 for two consecutive days). Warfarin sodium therapy should be initiated when appropriate (usually within 1-3 days of INNOHEP initiation).

As INNOHEP may theoretically affect the PT/INR, patients receiving both INNOHEP and warfarin should have blood for PT/INR determination drawn just prior to the next scheduled dose of INNOHEP.

Table 8 provides INNOHEP doses for the treatment of DVT with or without PE. It is necessary to calculate the appropriate INNOHEP dose for patient weights not displayed in Table 8.

An appropriately calibrated syringe should be used to assure withdrawal of the correct volume of drug from INNOHEP vials.

**Table 8. INNOHEP Weight-based Dosing for Treatment of Deep Vein Thrombosis With or Without Symptomatic Pulmonary Embolism**

Patient Body Weight in Pounds	DVT Treatment		Patient Body Weight in Kilograms
	175 IU/kg SC Once Daily 20,000 IU per mL		
	Dose (IU)	Amount (mL)	
68 - 80	6,000	0.3	31 – 36
81 - 94	7,000	0.35	37 – 42
95 - 107	8,000	0.4	43 – 48
108 - 118	9,000	0.45	49 – 53
119 - 131	10,000	0.5	54 – 59
132 - 144	11,000	0.55	60 – 65
145 - 155	12,000	0.6	66 – 70
156 - 168	13,000	0.65	71 – 76
169 - 182	14,000	0.7	77 – 82
183 - 195	15,000	0.75	83 – 88
196 - 206	16,000	0.8	89 – 93
207 - 219	17,000	0.85	94 – 99
220 - 232	18,000	0.9	100 – 105
233 - 243	19,000	0.95	106 – 110
244 - 256	20,000	1	111 – 116
257 - 270	21,000	1.05	117 – 122

To calculate the volume (mL) of an INNOHEP 175 anti-Xa IU per kg subcutaneous dose for treatment of deep vein thrombosis:

Patient weight (kg) X 0.00875 mL/kg = volume to be administered (mL) subcutaneously

**Administration**

INNOHEP is a clear, colorless to slightly yellow solution, and as with other parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

INNOHEP is administered by SC injection. It must not be administered by intramuscular or intravenous injection.

*Subcutaneous injection technique:* Patients should be lying down (supine) or sitting and INNOHEP administered by deep SC injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The injection site should be varied daily. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

## HOW SUPPLIED

**INNOHEP is available in a multiple dose 2 mL vial in the following packages:**

<b>Box of 1</b>	<b>2 mL vial (20,000 anti-Xa IU per mL) NDC 0056-0342-08</b>
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<b>Box of 10</b>	<b>2 mL vials (20,000 anti-Xa IU per mL) NDC 0056-0342-53</b>
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Store at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F)  
[See USP Controlled Room Temperature].

Keep out of the reach of children.

**Manufactured for:  
DuPont Pharma**

DuPont logo  
**Wilmington, DE 19880 USA**

**By:**

**Leo Pharmaceutical Products**

Leo logo  
**Ballerup, Denmark**

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