

Innohep[®]

(tinzaparin sodium injection)

Rx only

BRIEF SUMMARY—For more information, consult Full Prescribing Information.

For Subcutaneous (SC) 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).

CLINICAL STUDIES

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

In a randomized, multicenter, double-blind trial, INNOHEP (tinzaparin sodium injection) 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 thrombotic (TE) rate (recurrent DVT or PE) with INNOHEP was not significantly different than the rate with unfractionated heparin. The data are provided in the following table:

Mortality with INNOHEP was 4.6% (10 patients) and with heparin

Efficacy of Once Daily INNOHEP in the Treatment of Acute Deep Vein Thrombosis

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

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

² All randomized patients who received at least one dose of active study drug

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

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

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 to 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 in any tissue or organ of the body during therapy with INNOHEP. Hemorrhage in some cases has been reported to result in death or permanent disability. A hemorrhagic event should be seriously considered in the presence of an unexplained fall in hematocrit, hemoglobin, or blood pressure. 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/mm³ if baseline value ≥150,000/mm³, ≥50% decline if baseline <150,000/mm³) was identified in 1% of patients given INNOHEP; severe thrombocytopenia (platelet count less than 50,000/mm³) occurred in 0.13%.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, INNOHEP should be discontinued. Cases of thrombocytopenia with disseminated thrombosis also have been observed in clinical practice with heparins, and low molecular weight heparins, including tinzaparin sodium. Some of these cases were complicated by organ infarction with secondary organ dysfunction or limb ischemia, and have resulted in death.

Hypersensitivity: INNOHEP contains sodium metabisulfite, a sulfite which 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 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.

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, sulfapyrazone, dextran, NSAIDs including ketorolac tromethamine, ticlopidine, and clopidogrel), and thrombolytics. If coadministration 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 SC 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 SC doses up to 1800 IU/kg/day (about 2 times the maximum recommended human dose based on body surface area) and in rabbits at SC 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.

Cases of teratogenic effects that include cleft palate, optic nerve hypoplasia, and trisomy 21 (Down's) syndrome, and cutis aplasia of the scalp have been reported in infants of women who received INNOHEP during pregnancy.

Non-teratogenic Effects: There have been 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 (tinzaparin sodium injection); however, the incidence of major bleeding is low. In clinical trials, the definition of major bleeding included bleeding accompanied by ≥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 the following table:

Major Bleeding Events¹ in Treatment of Acute Deep Vein Thrombosis With or Without Pulmonary Embolism

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

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.

² 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.

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

Fatal or nonfatal hemorrhage from any tissue or organ can occur. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as, but are not limited to, paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; swelling; weakness; hypotension, shock, or coma. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis (see WARNINGS, Hemorrhage).

Thrombocytopenia: In clinical studies thrombocytopenia was identified in 1% of patients treated with INNOHEP. Severe thrombocytopenia (platelet count <50,000/mm³) 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 patients treated with INNOHEP.

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

Adverse Events: Adverse events with INNOHEP or heparin reported