

at a frequency of $\geq 1\%$ in clinical trials with patients undergoing treatment for proximal DVT with or without PE, are provided in the following table:

Other Adverse Events in Completed or Ongoing Trials: Other

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

Adverse Event	Treatment Group ¹	
	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

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.

adverse events reported at a frequency of $\geq 1\%$ in 4,000 patients who received INNOHEP in completed or ongoing clinical trials are listed by body system:

Body as a Whole: injection site hematoma, reaction unclassified. **Cardiovascular Disorders, General:** hypotension, hypertension. **Central and Peripheral Nervous System Disorders:** dizziness. **Gastrointestinal System Disorders:** flatulence, gastrointestinal disorder (not otherwise specified), dyspepsia. **Heart Rate and Rhythm Disorders:** tachycardia. **Myo-, Endo-, Pericardial and Valve Disorders:** angina pectoris. **Platelet, Bleeding and 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 the following tables:

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 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 Maculopapular rash Skin necrosis
Hematologic	Granulocytopenia Thrombocytopenia
Allergic reactions	Allergic reaction
Injection site reaction	Cellulitis
Neoplastic	Neoplasm

Other Serious Adverse Events Associated With INNOHEP from Post-Marketing Surveillance

Category	Serious Adverse Event
Organ dysfunction	Cholestatic hepatitis Increase in hepatic enzymes Peripheral ischemia Priapism
Bleeding-related	Hematoma Hemoptysis Ocular hemorrhage Rectal bleeding
Cutaneous reactions	Epidermal necrolysis Ischemic necrosis Stevens-Johnson syndrome Urticaria
Hematologic	Agranulocytosis Pancytopenia Thrombocythemia
Injection site reactions	Abscess Necrosis
Allergic reactions	Allergic purpura Angioedema
Fetal/neonatal	Cutis aplasia of the scalp 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.

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

OVERDOSEAGE

Symptoms/Treatment: Accidental overdosage of INNOHEP (tinzaparin sodium injection) may lead to bleeding complications (see **WARNINGS, Hemorrhage**). 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 SC 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.

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

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

Patient Body Weight in Pounds	DVT Treatment 175 IU/kg SC Once Daily 20,000 IU per mL		Patient Body Weight in Kilograms
	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 SC dose for treatment of deep vein thrombosis:

$$\text{Patient weight (kg)} \times 0.00875 \text{ mL/kg} = \text{volume to be administered (mL) subcutaneously}$$

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.

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.



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