# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

innohep 18,000 IU in 0.9 ml, solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tinzaparin sodium 20,000 anti-Factor Xa IU/ml

Excipients with known effect:
Sodium metabisulfite (1.83 mg/mL) and sodium (up to 40 mg/mL).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection. Colourless or slightly yellow aqueous solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of venous thrombosis and thromboembolic disease including deep vein thrombosis and pulmonary embolus in adults.

Extended treatment of venous thromboembolism and prevention of recurrences in adult patients with active cancer.

For some patients with pulmonary embolism (e.g. those with severe haemodynamic instability) alternative treatment, such as surgery or thrombolysis, may be indicated.

### 4.2 Posology and method of administration

Posology
*Treatment in adults*
175 anti-Xa IU/kg body weight given subcutaneously once daily for at least 6 days and until adequate oral anticoagulation is established.

*Extended treatment in adult patients with active cancer*
175 anti-Xa IU/kg body weight given subcutaneously once daily for a recommended treatment period of 6 months. The benefit of continued anticoagulation treatment beyond 6 months should be evaluated.

*Neuraxial anaesthesia*
Treatment doses of innohep (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia, see section 4.3. If neuraxial anaesthesia is planned, innohep should be discontinued at least 24 hours before the procedure is performed. innohep should not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after the catheter has been removed.

*Interchangeability*
For interchangeability with other LMWHs, see section 4.4.

*Paediatric population*
The safety and efficacy of innohep in children below 18 years have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

*Renal impairment*
If renal impairment is suspected, renal function should be assessed using a formula based on serum creatinine to estimate creatinine clearance level.

Use in patients with a creatinine clearance level < 30 ml/minute is not recommended, as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with creatinine clearance levels down to 20 ml/min. When required in these patients, innohep treatment can be initiated with anti-Xa monitoring, if the benefit outweighs the risk (see section 4.4: Renal impairment). In this situation, the dose of innohep should be adjusted, if necessary, based on anti-factor Xa activity. If the anti-factor Xa level is below or above the desired range, the dose of innohep should be increased or reduced respectively, and the anti-factor Xa measurement should be repeated after 3-4 new doses. This dose adjustment should be repeated until the desired anti-factor Xa level is achieved. For guidance, mean levels between 4 and 6 hours after administration in healthy volunteers and patients without severe renal insufficiency have been between 0.5 and 1.5 IU/anti-factor Xa IU/ml. Anti-factor Xa activity determinations were by a chromogenic assay.

*Elderly*
innohep should be used in the elderly in standard doses. Precaution is recommended in the treatment of elderly patients with renal impairment. If renal impairment is suspected, see section 4.2: Renal impairment and section 4.4: Renal impairment.

Method of administration
Parenteral products should be inspected visually prior to administration. Do not use if cloudiness or precipitate is observed. The liquid may turn yellow by storage but is still suitable.

Administration is by subcutaneous injection. This can be done in abdominal skin, the outer side of the thigh, lower back, upper leg or upper arm. Do not inject in the area around the navel, near scars or in wounds. For abdominal injections, the patient should be in supine position, alternating the injections between left and right side. The air-bubble within the syringe should not be removed. During the injection, the skin should be held in a fold.

Doses are administered in 1,000 IU increments facilitated by the 0.05 ml graduations on the syringes. The calculated dose, based on the patient's body weight, should therefore be rounded up or down as appropriate. If necessary, any excess volume should be expelled, to achieve the appropriate dosage before SC injection.

| **Guide to appropriate dosages for different body weights - 175 IU/kg body weight subcutaneously once daily** | | | |
|---|---|---|---|
| | **kg*** | **International units (IU)** | **Injection volume (ml)** |
| **20,000 IU/ml in graduated syringes** | 32-37 | 6,000 | 0.30 |
| | 38-42 | 7,000 | 0.35 |
| | 43-48 | 8,000 | 0.40 |
| | 49-54 | 9,000 | 0.45 |
| | 55-59 | 10,000 | 0.50 |
| | 60-65 | 11,000 | 0.55 |
| | 66-71 | 12,000 | 0.60 |
| | 72-77 | 13,000 | 0.65 |
| | 78-82 | 14,000 | 0.70 |
| | 83-88 | 15,000 | 0.75 |
| | 89-94 | 16,000 | 0.80 |
| | 95-99 | 17,000 | 0.85 |
| | 100-105 | 18,000 | 0.90 |

*For patients weighing < 32 kg or > 105 kg, the same calculation as above should be used to establish the appropriate dose/volume

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Current or history of immune-mediated heparin-induced thrombocytopenia (type II) (see section 4.4).

Active major haemorrhage or conditions predisposing to major haemorrhage. Major haemorrhage is defined as fulfilling any one of these three criteria:

a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome),
b) causes a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or
c) leads to transfusion of two or more units of whole blood or red cells.

Septic endocarditis.

Treatment doses of innohep (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia. If neuraxial anaesthesia is planned, innohep should be discontinued at least 24 hours before the procedure is performed. innohepshould not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after the catheter has been removed. Patients should be closely monitored for signs and symptoms of neurological injury.

**4.4 Special warnings and precautions for use**

Neuraxial anaesthesia
In patients undergoing epidural/spinal anaesthesia or spinal puncture, the prophylactic use of heparins/low molecular weight heparins (LMWH) may be very rarely associated with epidural/spinal haematoma resulting in prolonged or permanent paralysis. This risk is increased by the use of: epidural/spinal catheter for anaesthesia; the concomitant use of drugs affecting haemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants; traumatic or repeated neuraxial puncture.

Should a physician decide to administer anticoagulation in the context of epidural/spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits (numbness and weakness in lower limbs), bowel and/or bladder dysfunction. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to immediately inform a nurse or a clinician if they experience any of these symptoms.

If signs or symptoms of epidural/spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

Haemorrhage
Caution is advised when administering innohep to patients at risk of haemorrhage. For patients at risk of major haemorrhage, see section 4.3. The combination with medicinal products affecting platelet function or the coagulation system should be avoided or carefully monitored (see section 4.5).

Intramuscular injections
innohep must be administered subcutaneously and not via intramuscular injection. Due to the risk of haematoma, concomitant intramuscular injections should be avoided.

Heparin-induced thrombocytopenia
Platelet count should be measured before the start of treatment and periodically thereafter because of the risk of immune-mediated heparin-induced thrombocytopenia (type II). innohep must be discontinued in patients who develop immune-mediated heparin-induced thrombocytopenia (type II) (see sections 4.3 and 4.8). Platelet counts will usually normalise within 2 to 4 weeks after withdrawal.
Regular monitoring of platelet count also applies to extended treatment for cancer-associated thrombosis, especially during the first month, considering that cancer and its treatments such as chemotherapy may also cause thrombocytopenia.

Hyperkalaemia
Heparin products can suppress adrenal secretion of aldosterone, leading to hyperkalaemia. Risk factors include diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium at pre-treatment, concomitant therapy with drugs that may elevate plasma potassium, and long-term use of innohep. In patients at risk, potassium levels should be measured before starting innohep and monitored regularly thereafter. Heparin-related hyperkalaemia is usually reversible upon treatment discontinuation, though other approaches may need to be considered if innohep treatment is considered lifesaving (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance).

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

Renal impairment
Use in patients with a creatinine clearance level <30 ml/minute is not recommended, as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with creatinine clearance levels down to 20 ml/minute. When required in these patients, innohep treatment can be used cautiously with anti-Xa monitoring, if the benefit outweighs the risk (see section 4.2). Although anti-Xa monitoring remains a poor predictor of haemorrhage risk, it is the most appropriate measure of the pharmacodynamic effects of innohep.

Elderly
Elderly are more likely to have reduced renal function (see section 4.4: Renal impairment) therefore caution should be exercised when prescribing innohepto the elderly.

Interchangeability
Low molecular weight heparins should not be used interchangeably because of differences in pharmacokinetics and biological activities. Switching to an alternative low molecular weight heparin, especially during extended use, must be exercised with particular caution and specific dosing instructions for each proprietary product must be followed.

Excipient warnings
This formulation of innohep contains sodium metabisulfite. In rare cases, metabisulfites may cause severe hypersensitivity reactions, including bronchospasm.
innohep formulations containing sodium metabisulfite must be used with caution in patients with asthma.

This medicinal product contains up to 40 mg sodium per mL. The amount 40 mg is equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

**4.5 Interaction with other medicinal products and other forms of interaction**

The anticoagulant effect of innohep may be enhanced by other drugs affecting the coagulation system, such as those inhibiting platelet function (e.g. acetylsalicylic acid and other non-steroidal anti-inflammatory drugs), thrombolytic agents, vitamin K antagonists, activated protein C, small molecule anti-Xa and IIa inhibitors. Such combinations should be avoided or carefully monitored (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

Pregnancy
Anticoagulant treatment of pregnant women requires specialist involvement.

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

A large amount of data on pregnant women (more than 2,200 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of tinzaparin. Tinzaparin does not cross the placenta. innohep can be used during all trimesters of pregnancy if clinically needed.

*Epidural anaesthesia*
Due to the risk of spinal haematoma, treatment doses of innohepare contraindicated in patients who receive neuraxial anaesthesia (see section 4.3). Therefore, epidural anaesthesia in pregnant women should always be delayed until at least 24 hours after administration of the last treatment dose of innohep. Prophylactic doses may be used as long as a minimum delay of 12 hours is allowed between the last administration of innohepand the needle or catheter placement.

*Pregnant women with prosthetic heart valves*
Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of innohep and other low molecular weight heparins. innohepcannot be recommended for use in this population.
In the absence of clear dosing, efficacy and safety information in this circumstance, any attempt to anti-coagulate such patients must only be undertaken by medical practitioners with expertise and experience in this clinical area, and only if no safer alternative is available.

Breast-feeding
Animal data indicate that innohep excretion into breast milk is minimal.
It is unknown whether tinzaparin is excreted into human milk. Although oral absorption of low molecular weight heparins is unlikely, a risk to the breast-fed child cannot be excluded.

In patients at risk the incidence of venous thromboembolism is particularly high during the first six weeks after child birth.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from innohep therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no clinical studies with innohep regarding fertility.

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

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

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

Immune-mediated heparin-induced thrombocytopenia (type II) largely manifests within 5 to 14 days of receiving the first dose. Furthermore, a rapid onset form has been described in patients previously exposed to heparin. innohep must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia (see section 4.4).

In rare cases, innohep may cause hypoaldosteronism associated with hyperkalaemia and metabolic acidosis. Patients at risk include those with diabetes mellitus or renal impairment (see section 4.4).

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

Priapism has been reported rarely.

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and from spontaneous reporting.

Undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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

| **Blood and lymphatic system disorders** | |
|---|---|
| Common ≥1/100 and < 1/10 | Anaemia (incl. haemoglobin decreased) |
| Uncommon ≥1/1,000 and <1/100 | Thrombocytopenia (type I) (incl. platelet count decreased) |
| Rare ≥1/10,000 and <1/1,000 | Heparin induced thrombocytopenia (type II) Thrombocytosis |
| **Immune system disorders** | |
| Uncommon ≥1/1,000 and <1/100 | Hypersensitivity |
| Rare ≥1/10,000 and <1/1,000 | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | |
| Rare ≥1/10,000 and <1/1,000 | Hypoaldosteronism associated with hyperkalaemia and metabolic acidosis |
| **Vascular disorders** | |

| | |
|---|---|
| Common ≥1/100 and < 1/10 | Haemorrhage<br>Haematoma |
| Uncommon ≥1/1,000 and <1/100 | Bruising, ecchymosis and purpura |
| **Hepatobiliary disorders** | |
| Uncommon ≥1/1,000 and <1/100 | Hepatic enzyme increased (incl. increased transaminases, ALT, AST and GGT) |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon ≥1/1,000 and <1/100 | Dermatitis (incl. allergic dermatitis and bullous)<br>Rash<br>Pruritus |
| Rare ≥1/10,000 and <1/1,000 | Toxic skin eruption (including Stevens-Johnson syndrome)<br>Skin necrosis<br>Angioedema<br>Urticaria |
| **Musculoskeletal and connective tissue disorders** | |
| Rare ≥1/10,000 and <1/1,000 | Osteoporosis (in connection with long-term treatment) |
| **Reproductive system and breast disorders** | |
| Rare ≥1/10,000 and <1/1,000 | Priapism |
| **General disorders and administration site conditions** | |
| Common ≥1/100 and < 1/10 | Injection site reaction (incl. injection site haematoma, haemorrhage, pain, pruritus, nodule, erythema and extravasation) |

Patients with cancer on extended treatment
In a trial of patients with cancer on extended (6 months) treatment with innohep, the overall frequency of adverse reactions was comparable to that seen in other patients treated with innohep. Patients with cancer generally have an increased risk of haemorrhage, which is further influenced by older age, comorbidities, surgical interventions and concomitant medications. Thus, as expected, the incidence of haemorrhagic events was higher than previously observed in short-term use, and similar to the rates seen with extended use of anticoagulants in patients with cancer.

Paediatric population
Limited information derived from one study and postmarketing data indicates that the pattern of adverse reactions in children and adolescents is comparable to that in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

### 4.9 Overdose

Haemorrhage is the main complication of overdose. Due to the relatively short pharmacokinetic half-life of innohep (see section 5.2), minor haemorrhages can be managed conservatively following treatment discontinuation. Serious haemorrhage may require the administration of the antidote protamine sulfate. Patients should be carefully monitored.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Heparin group, ATC code: B01AB10

Mechanism of action
innohep is a low molecular weight heparin of porcine origin with an anti-Xa/anti-IIa ratio between 1.5 and 2.5. innohep is produced by enzymatic depolymerisation of conventional unfractionated heparin. Like conventional heparin, innohep acts as an anticoagulant by potentiating antithrombin III's inhibition of activated coagulation factors, primarily factor Xa.

The biological activity of innohep is standardised against the current "International standards for low molecular weight heparins", and expressed in anti-Xa international units (IU).

The anti-Xa activity of innohep is not less than 70 and not more than 120 IU/mg. The anti-IIa activity of innohep is approximately 55 IU/mg. The characteristic value of the mass-average molecular mass of innohep is about 6,500 daltons.

Pharmacodynamic effects
innohep has a high antithrombin activity (anti-IIa), a low anti-Xa/anti-IIa ratio and an inhibition of thrombin formation with almost the same potency as unfractionated heparin. In addition to its anti-Xa/IIa activity, induction of TFPI (Tissue Factor Pathway Inhibitor) has been identified in patients.

Clinical efficacy and safety
Initial treatment of acute deep vein thrombosis and pulmonary embolism
In a double-blind clinical study, innohep (175 IU/kg subcutaneously once daily) was compared with dose-adjusted heparin administered by continuous intravenous infusion for the initial treatment of patients with proximal venous thrombosis. All patients started oral anticoagulation therapy with warfarin on day 2, and were treated with innohep or heparin for at least six days. Six of 213 patients receiving innohep (2.8%) and 15 of 219 patients receiving heparin (6.9%) had a recurrent episode of venous thromboembolism (VTE) ($p = 0.07$) during the study's 3-month follow-up period. Severe haemorrhages that were determined to be associated with the initial treatment occurred in one patient who received innohep (0.5%) and in 11 patients who received heparin (5.0%), corresponding to a 91% reduction in risk ($p = 0.006$). There were 10 deaths in the innohep group (4.7%) and 21 in the heparin group (9.6%), which corresponds to a risk reduction of 51% ($p = 0.049$).

In an unblinded study (THESEE), 612 patients with symptomatic pulmonary embolism were randomised to innohep (175 IU/kg subcutaneously once daily) or dose-adjusted intravenous heparin, during the first 8 days of treatment. Oral anticoagulation therapy was introduced on days 1-3 and was administered for at least 3 months. Based on a combined endpoint (recurrent VTE, severe haemorrhage and death), 9 of 308 patients in the heparin group (2.9%) and 9 of 304 patients in the innohep group (3.0%) had achieved at least one endpoint on day 8 (absolute difference: -0.1%; 95% KI: -2.7 to 2.6).

Prolonged treatment of acute deep vein thrombosis and pulmonary embolism
In a sub-analysis ("Main-LITE cancer") of a randomised, open-label clinical study, innohep (175 IU/kg subcutaneously once daily) was compared with warfarin for 3 months of treatment in patients with proximal venous thrombosis. Of the 200 patients who had cancer (100 patients in each group), there were more cases of recurrent VTE after 12 months in the warfarin group (16%) compared with the innohep group (7%) (absolute difference: -9.0; 95% CI: -21.7 to -0.7). During 3 months, severe haemorrhage was reported in 7% of patients in both of the groups. At one year, mortality was 47% in both groups.

In an open-label, randomised study of 241 patients with acute proximal deep vein thrombosis (DVT), 69 of whom had cancer, innohep (175 IU/kg subcutaneously once daily) was compared with an oral vitamin K antagonist (VKA), during 6 months of DVT treatment. In patients with cancer, the incidence of recurrent VTE was lower in the innohep group (2/36 [5.5%]) compared with seven of 33 [21.2%]). One severe haemorrhage occurred in the innohep group, compared to 3 in the VKA group.

In a controlled, open-label, randomised clinical study (CATCH), the efficacy and safety of innohep were compared to warfarin after 6 months of treatment of acute, symptomatic DVT, or pulmonary embolism in patients with active cancer. The study included 900 patients with renal function corresponding to a creatinine clearance (CrCl) of down to 20 mL/min. Patients with a thrombocyte count below 50 × 109/L were not included in the study. The patients in the innohep group received full-dose innohep injections (175 IU/kg subcutaneously) once daily throughout the treatment period (6 months) and were compared with patients receiving innohep once daily for 5–10 days, followed by dose-adjusted warfarin (INR: 2.0–3.0) for 6 months. Efficacy outcomes (DVT in the lower extremities and pulmonary embolism) and safety outcomes (bleeding events, heparin-induced thrombocytopaenia and death) were assessed by a blinded committee. Recurrent VTE occurred in 31 of 449 patients in the innohep group and 45 of 451 patients in the warfarin group (6-month cumulative incidence: 7.2% for innohep compared to 10.5% for warfarin; hazard ratio [HR]: 0.65; 95% CI: 0.41–1.03; $p = 0.07$). Symptomatic DVT occurred in 12 patients in the innohep group and in 24 patients in the warfarin group (HR: 0.48; 95% CI: 0.24–0.96; $p = 0.04$) There was no significant difference in severe bleeding events (HR: 0.89; 95% CI: 0.40–1.99; $p = 0.77$), or mortality from all causes (1.08; 95% CI: 0.85–1.36; $p = 0.54$), but on the other hand there was a statistically-significant reduced risk of clinically-relevant, non-severe bleeding in the innohep group compared to the warfarin group (HR: 0.58; 95% CI: 0.40–0.84; $p = 0.004$).

In a pre-specified secondary analysis of the CATCH Study, where competing outcomes were used for a regression analysis of the time to first clinically-relevant bleeding (CRB; severe and clinically-relevant, non-severe events), the risk of having at least one CRB event during the 6-month study was significantly lower in the innohep group (n = 60/449) than in the warfarin group (n = 78/451), HR: 0.64; 95% CI: 0.45–0.89; $p = 0.009$. The cumulative incidence rates of CRB in the two groups differed almost immediately and continued to show a benefit for innohep patients during the six-month treatment period (see Figure 1). In a multivariate analysis for all treatment groups, the risk of CRB was found to increase with age > 75 years (HR 1.83) and intracranial malignancy (HR 1.97).

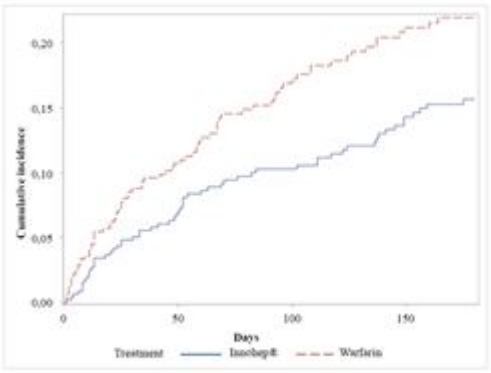


Figure 1

In a secondary analysis of the CATCH Study, the effect of renal impairment (RI, defined as glomerular filtration rate [GFR] < 60 m /min/1.73 m2) was assessed based on the efficacy and safety of anticoagulation therapy in patients with cancer-associated thrombosis. The study population for this analysis included 864 patients (96%) for whom a GFR value from a central laboratory was available at the time of randomisation. Of these, 131 patients (15%) had baseline renal impairment (69 in the innohep group and 62 in the warfarin group). Renal impairment in patients with cancer-associated thrombosis receiving anticoagulation therapy was associated with a statistically-significant increase in recurrent VTE and severe haemorrhage, but no significant increase in clinically-relevant bleeding (CRB) or mortality was observed. Long-term treatment with innohep at full therapeutic dose, without dose adjustment in patients with renal impairment, did not increase the incidence of recurrent VTE, CRB, severe haemorrhage or mortality compared to warfarin.

A prospective, open-label clinical study ("TICAT") included 247 patients with active cancer and newly diagnosed DVT and/or pulmonary embolism. The average duration of treatment with innohep (175 IU/kg subcutaneously once daily) was 15.6 (SD: 13.2) months. The incidence of recurrent VTE decreased during the study from 4.5% during the first 6 months (95% CI: 2.2% –7.8%) to 1.1% (95% CI: 0.1% –3.9%) during months 7–12 (p = 0.08). The incidence of clinically-relevant bleeding was 0.9% per patient month (95% CI: 0.5% –1.6%) during the first 6 months and 0.6% per patient month (95% CI: 0.2% –1.4%) during months 7–12. One patient (0.4%) died due to recurrent pulmonary embolism and 2 patients (0.8%) died due to haemorrhage.

Special patient populations

Population with renal impairment
The safety profile of innohep (175 IU/kg once daily) for up to 30 days was investigated in a study involving 200 elderly inpatients with a CrCl of > 20 mL/min. The anti-Xa activity in plasma was measured regularly. The mean age was 85.2 years (range: 70 to 102) and the average CrCl was 51.2 ± 22.9 mL/min. One death was suspected of having been related to anticoagulation therapy. Three severe bleeding episodes (1.5%) were reported. Heparin-induced thrombocytopaenia was confirmed in 2 patients (1%). No correlation was observed between anti-Xa activity and CrCl or age.

**5.2 Pharmacokinetic properties**

The absolute bioavailability based on anti-Xa activity after subcutaneous administration is approximately 90% and the time to reach maximal activity is 4-6 hours. The terminal elimination half-life is approximately 3.7 hours. Due to the long half-life of the pharmacological effect for innohep, once daily administration is sufficient.

The pharmacokinetic activities of tinzaparin have been studied in pregnancy. Data from sequential pharmacokinetic monitoring in 55 pregnancies suggests that pharmacokinetic properties do not differ from the non-pregnant state. There was a small, but non-statistically significant, decrease in anti-Xa levels with advancing gestation.

*Paediatric population*
Preliminary data on the use of tinzaparin suggest that younger children including neonates and infants clear tinzaparin faster and therefore might require higher doses than older children. However, data are not sufficient to allow for dosing recommendations, see section 4.2.

**5.3 Preclinical safety data**

No additional data

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium metabisulfite

Sodium hydroxide (for pH-adjustment)
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

3 years
Any portion of the contents not used at once should be discarded.
The liquid may turn yellow in storage but this does not affect product quality.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

1 ml prefilled variable dose graduated syringe made of colourless glass of hydrolytic resistance type 1 assembled with a stainless steel needle (needle length ~ 12.7 mm), sealed with a plunger stopper made of chlorobutyl or bromobutyl rubber type I, a needle shield protective cap made of styrene butadiene or polyisoprene rubber and a plastic needle safety device.

Syringe contains 0.9 ml solution.

Supplied in packs of 2, 6 or 10 syringes.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Do not use if cloudiness or particles are visible in the liquid. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Leo Laboratories Limited
285 Cashel Road
Dublin 12
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA0046/060/004

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 1997
Date of last renewal: 23 January 2007

## 10 DATE OF REVISION OF THE TEXT