SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

innohep Syringe 20,000 IU/ml

or

tinzaparin sodium Syringe 20,000 IU/ml

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 (in total < 23 mg/dose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

1 ml syringe holding a colourless to straw coloured liquid, free from turbidity and from matter that deposits on standing.

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 tinzaparin sodium (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia, see section 4.3. If neuraxial anaesthesia is planned, tinzaparin sodium should be discontinued at least 24 hours before the procedure is performed. Tinzaparin sodium 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 tinzaparin sodium 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, tinzaparin sodium 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 tinzaparin sodium 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 tinzaparin sodium 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
Tinzaparin sodium 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 2 or more units of whole blood or red blood cells.

- Septic endocarditis.

- Treatment doses of tinzaparin sodium (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia. If neuraxial anaesthesia is planned, tinzaparin

sodium should be discontinued at least 24 hours before the procedure is performed. Tinzaparin sodium should 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

Haemorrhage
Caution is advised when administering tinzaparin sodium 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
Tinzaparin sodium should not be administered by intramuscular injection due to the risk of haematoma. Due to the risk of haematoma, concomitant intramuscular injections should also 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). Tinzaparin sodium must be discontinued in patients who develop immune-mediated heparin-induced thrombocytopenia (type II) (see section 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 tinzaparin sodium. In patients at risk, potassium levels should be measured before starting tinzaparin sodium and monitored regularly thereafter. Heparin-related hyperkalaemia is usually reversible upon treatment discontinuation, though other approaches may need to be considered (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance).

Prosthetic heart valves
There have been no adequate studies to assess the safe and effective use of tinzaparin sodium in preventing valve thrombosis in patients with prosthetic heart valves; therefore no dosage recommendations can be given. High doses of tinzaparin sodium (175 IU/kg) may not be sufficient prophylaxis to prevent valve thrombosis in patients with prosthetic heart valves. The use of tinzaparin sodium 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, tinzaparin sodium 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 tinzaparin sodium.

Elderly
Elderly are more likely to have reduced renal function (see Section 4.4: Renal impairment); therefore caution should be exercised when prescribing tinzaparin sodium to 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

Tinzaparin sodium 20,000 IU/ml contains sodium metabisulfite. Metabisulfites may rarely cause severe hypersensitivity reactions and bronchospasm. Tinzaparin sodium 20,000 IU/ml must be used with caution in patients with asthma.

This medicinal product contains up to 40 mg sodium per mL, equivalent up 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, direct factor 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 nor 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 innohep (175 IU/kg) are contraindicated in patients who receive neuraxial anaesthesia. 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 innohep and the needle or catheter placement.

Pregnant women with prosthetic heart valves:
Therapeutic failures and maternal death have been reported in pregnant women with prosthetic heart valves on full anticoagulant doses of innohep and other low molecular weight heparins. In the absence of clear dosing, efficacy and safety information in this circumstance, innohep is not recommended for use in pregnant women with prosthetic heart valves.

Breast-feeding
In patients at risk, the incidence of venous thromboembolism is particularly high during the first 6 weeks after child birth.

The passage of tinzaparin into human breast milk is expected to be very low. The oral absorption of any trace amount of tinzaparin sodium in the breast milk to the infant is very unlikely. Tinzaparin can be used during breastfeeding.

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 or 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. Immune-mediated heparin-induced thrombocytopenia (type II) may be associated with arterial and venous thrombosis. Tinzaparin sodium must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia (see section 4.4).

In rare cases, tinzaparin sodium may cause hyperkalaemia due to hypoaldosteronism. 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.

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 to < 1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Common	Anaemia (incl. haemoglobin decreased)
Uncommon	Thrombocytopenia (type I) (incl. platelet count decreased)
Rare	Heparin-induced thrombocytopenia (type II) Thrombocytosis
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Anaphylactic reaction
Metabolism and nutrition disorders	
Rare	Hyperkalaemia
Vascular disorders	
Common	Haemorrhage Haematoma
Uncommon	Bruising, ecchymosis and purpura
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased (incl. increased transaminases, ALT, AST and GGT)
Skin and subcutaneous tissue disorders	
Uncommon	Dermatitis (incl. dermatitis allergic and bullous) Rash Pruritus
Rare	Toxic skin eruption (including Stevens-Johnson syndrome) Skin necrosis Angioedema Urticaria
Musculoskeletal and connective tissue disorders	
Rare	Osteoporosis (in connection with long-term treatment)
Reproductive system and breast disorders	
Rare	Priapism
General disorders and administration site conditions	
Common	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 tinzaparin sodium, the overall frequency of adverse reactions was comparable to that seen in other patients treated with tinzaparin sodium. 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Haemorrhage is the main complication of overdose. Due to the relatively short 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.

Any hypovolaemia should be actively managed. Transfusion of fresh plasma may be used, if necessary. Plasma anti-Factor Xa and anti-Factor IIa activity should be measured during the management of overdose situations. Usually, the anticoagulant effects will have reduced to negligible levels after 24 hours, but treatment should be according to the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Pharmacodynamic effects
Tinzaparin 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.
Tinzaparin has a high average molecular weight (see Mechanism of action above).

Clinical efficacy and safety
Initial treatment of acute deep vein thrombosis and pulmonary embolism
In a double-blind clinical study, tinzaparin (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 tinzaparin or heparin for at least six days. Six of 213 patients receiving tinzaparin (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 tinzaparin (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 tinzaparin group (4.7%) and 21 in the heparin group (9.6%), which corresponds to a risk reduction of 51% ($p = 0.049$).

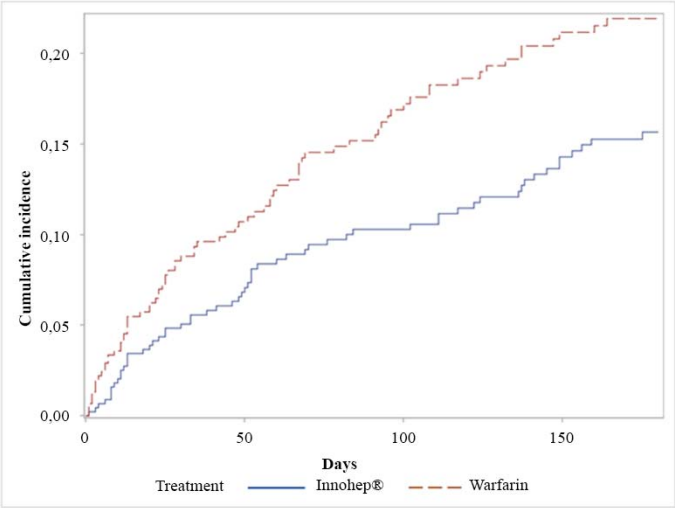
In an unblinded study (THESEE), 612 patients with symptomatic pulmonary embolism were randomised to tinzaparin (175 IU/kg subcutaneously once daily) or dose-adjusted intravenous heparin, during the first 8 days of treatment. Oral anticoagulation therapy was introduced on days 1-3 and was administered 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 tinzaparin group (3.0%) had achieved at least one endpoint on day 8 (absolute difference: -0.1%; 95% Kl: -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, tinzaparin (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 tinzaparin 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 a controlled, open-label, randomised clinical study (CATCH), the efficacy and safety of tinzaparin 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 50×10^9/L were not included in the study. The patients in the tinzaparin group received full-dose tinzaparin injections (175 IU/kg subcutaneously) once daily throughout the treatment period (6 months) and were compared with patients receiving tinzaparin 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 tinzaparin group and 45 of 451 patients in the warfarin group (6-month cumulative incidence: 7.2% for tinzaparin 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 tinzaparin group and in 24 patients in the warfarin group (HR: 0.48; 95% Cl: 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 tinzaparin 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 tinzaparin group (n = 60/449) than in the warfarin group (n = 78/451), HR: 0.64; 95% Cl: 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 tinzaparin 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

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 tinzaparin (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
In a prospective study, it was investigated whether tinzaparin (175 anti-Xa IU/kg subcutaneously once daily) accumulated during 10 days of treatment in 30 inpatients older than 70 years of age, who received a therapeutic dose for acute thromboembolic disease. Plasma levels of anti-Xa and anti-IIa, as well as activated partial thromboplastin time (APTT), were determined before the first injection at peak levels, i.e. 5 hours after the second injection (day 2) and on days 5, 7 and 10. The patients were on average 87 years old (range: 71-96 years of age), had a body weight of 62.7 kg (range: 38-90 kg) and a CrCl mean of 40.6 ± 15.3 mL/min (range: 20-72 mL/min). Since no patient had an anti-Xa activity above 1.5 IU/mL, no dose adjustment was made. The average maximum anti-Xa level was 0.66 ± 0.20 IU/mL (range: 0.26–1.04) on day 2. There was no progressive increase in anti-Xa or anti-IIa activity after repeated daily treatment with tinzaparin for 10 days. No correlation was found between anti-Xa and anti-IIa activities and age, weight or CrCl. No severe bleeding occurred and there were no thromboembolic complications or deaths.

The safety profile of tinzaparin (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 mean age was 85.2 years (range: 70 to 102) and the average CrCl was 51.2 ± 22.9 mL/min. The anti-Xa activity in plasma was measured regularly. No correlation was observed between anti-Xa activity and CrCI or age but 13% of patients had a dose reduction due to anti-Xa activity ≥1.4 IU/ml. 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%).

A secondary analysis of the CATCH Study assessed the effect of renal impairment (RI, defined as glomerular filtration rate [GFR] < 60 m /min/1.73 m^2) 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 tinzaparin group and 62 in the warfarin group). Renal impairment 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 tinzaparin 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.

5.2 Pharmacokinetic properties

The absolute bioavailability based on anti-Xa activity after subcutaneous administration is approximately 90% and time to reach maximal activity is 4-6 hours.

Tinzaparin has a high, average molecular weight. Its elimination is dose-dependent and is a combination of a saturable elimination by the reticuloendothelial system and a non-saturable elimination via the renal route.

In healthy volunteers, the terminal elimination half-life following SC administration of tinzaparin at a dose of 4,500 IU or 175 IU/kg is approximately 3-4 hours based on anti-Xa activity.

Special patient populations
Pregnant women
The pharmacokinetic activity of tinzaparin has been studied in pregnant women. Data from sequential pharmacokinetic monitoring of 55 pregnant women who received tinzaparin at a dose of up to 175 IU/kg indicated that there was little or no influence of pregnancy on the pharmacokinetic properties of tinzaparin when compared with non-pregnant women.

Renal impairment
In patients treated with tinzaparin sodium (175 IU/kg), a population pharmacokinetic analysis showed no correlation between anti-Xa activity and creatinine clearance in moderate (30-50 mL/min) and severe (<30 mL/min) renal impairment. No clinically significant accumulation was observed in patients with creatinine clearance ≥20 mL/min.

The observed half-life of an intravenous bolus injection of 75 IU/kg that was administered just before dialysis was shorter (2.3 hours) than subcutaneous administration of the same dose on an off-dialysis day (3.9 hours).

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
There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium metabisulfite

Sodium hydroxide

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.

Contains no bactericide, any portion of the contents not used at once should be discarded together with the syringe.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

1 ml pre-filled variable dose graduated syringe (glass Type I) with protective cap, plunger and needle safety device containing:

0.4 ml (8,000 anti-Factor Xa IU)
0.5 ml (10,000 anti-Factor Xa IU)
0.6 ml (12,000 anti-Factor Xa IU)
0.7 ml (14,000 anti-Factor Xa IU)
0.8 ml (16,000 anti-Factor Xa IU)
0.9 ml (18,000 anti-Factor Xa IU)

Pack sizes: 2, 6 or 10 syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

LEO Laboratories Limited

Maidenhead

Berkshire

SL6 3UD

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00043/0197

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

03/12/2025