Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

innohep 2,500 IU, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tinzaparin sodium 10,000 anti-Factor Xa IU/ml

Excipients with known effect:
Sodium (in total < 23 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

Prophylaxis of venous thromboembolism in adult patients undergoing surgery, particularly orthopaedic, general or oncological surgery.

Prophylaxis of venous thromboembolism in non-surgical adult patients immobilised due to acute medical illness including: acute heart failure, acute respiratory failure, severe infections, active cancer, as well as exacerbation of rheumatic diseases.

Prevention of clotting in extracorporeal circuits during haemodialysis and haemofiltration in adults.

4.2 Posology and method of administration

Posology

Prophylaxisof thromboembolic events in adults:
Administration is by subcutaneous injection.
Surgical patients at moderate risk of thromboembolic events:
3,500 anti-Xa IU given SC 2 hours before surgery and then once daily for as long as the patient is considered to be at risk of VTE.
Surgical patients at high risk of thromboembolic events e.g. undergoing orthopaedic or cancer surgery:
4,500 anti-Xa IU given SC 12 hours before surgery and then once daily for as long as the patient is considered to be at risk of VTE.
Non-surgical patients immobilised due to acute medical illness:
3,500 anti-Xa IU given SC once daily in patients at moderate risk of VTE, or 4,500 anti-Xa IU given SC once daily in patients at high risk of VTE. Administration should continue for as long as the patient is considered to be at risk of VTE.

Neuraxial anaesthesia
Caution is advised when performing neuraxial anaesthesia or lumbar puncture in patients receiving prophylactic doses of innohep, see section 4.4: Neuraxial anaesthesia. If neuraxial anaesthesia is planned, a minimum delay of 12 hours should be allowed between the last prophylactic dose and the needle or catheter placement. innohep should not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after the catheter has been removed. Thus, the 2 hours preoperative initiation of thromboprophylaxis with innohep is not compatible with neuraxial anaesthesia.

Haemodialysis and haemofiltration in adults:
Duration of 4 hours or less:
A bolus injection of 2,000 to 2,500 anti-Xa IU at the start of dialysis.

Duration of more than 4 hours:
A bolus injection of 2,500 anti-Xa IU at the start of dialysis/filtration, followed by 750 anti-Xa IU/hour as a continuous infusion.
Dose adjustment:
If necessary, the bolus dose may be increased or decreased gradually in increments of 500 anti-Xa IU until a satisfactory response is obtained. The usual dose is within 2,000 - 4,500 anti-Xa IU.
If case of concomitant transfusion of blood or concentrated red corpuscles, an extra bolus injection of 500 - 1,000 anti-Xa IU can be administered.

Dose monitoring:
Determination of plasma anti-Xa activity can be used to monitor the innohep dose during haemodialysis/haemofiltration. The plasma anti-Xa level should be approximately 0.5 anti-Xa IU/ml one hour after administration.

Interchangeability
For interchangeability with other LMWHs, see section 4.4.

Special populations
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 administration can be initiated with anti-Xa monitoring, if the benefit outweighs the risk (see section 4.4: Renal impairment).

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.

Weight
For patients with very low or very high body weight, 50 anti-Xa IU per kg body weight once daily may be considered as an alternative to fixed dosing. For surgical patients, the first dose is given SC 2 hours before surgery. The administration should continue once daily for as long as the patient is considered to be at risk of VTE.

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 during storage but is still useable.

Administration is by subcutaneous injection when given as prophylaxis of thromboembolic events in adults. 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 a supine position, alternating the injections between the 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.

For haemodialysis, the dose of innohep should be given into the arterial side of the dialyser or intravenously. The dialyser can be primed by flushing with 500–1,000 ml isotonic sodium chloride (9 mg/ml) containing 5,000 anti-Xa IU innohep per litre.

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

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 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.

In decision-making on the interval between the last administration of heparin/low molecular weight heparin at prophylactic doses and the placement or removal of an epidural/spinal catheter, the pharmacokinetic profile of tinzaparin sodium (see section 5.2) and the patient profile should be taken into account.

A minimum delay of 12 hours should be allowed between the last prophylactic dose of innohep and the needle or catheter placement. For continuous techniques, a similar delay should be observed before removing the catheter. Moreover, innohep should not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after the catheter has been removed.

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.

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 valves
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 administration 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 innohep 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
This medicinal product contains less than 1 mmol sodium (23 mg) per mL, i.e. essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

The anticoagulant effect of innohepmay 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. 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 (see section 4.4).

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. innohep cannot 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 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 dermatitis) Rash Pruritus
Rare ≥1/10,000 and <1/1,000	Toxic skin eruption (including Stevens-Johnson syndrome) Skin necrosis Angioedema 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)

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 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
Venous thromboembolism prophylaxis in moderate-risk surgery

In a double-blind, multi-centre study that included 1,290 patients who underwent general surgery, the patients were randomly assigned to groups that received either two doses of innohep (2,500 IU; n = 431 or 3,500 IU; n = 430), or heparin 5,000 IU bolus dose (n = 429), to prevent deep vein thrombosis (DVT). The type of surgery was mostly abdominal (71%), gynaecological (13%) and urological (10%) and 57% of all patients were aged > 60 years. The treatments were administered subcutaneously 2 hours before surgery and continued for 7 to 10 days, and patients who required long-term prophylaxis continued with heparin after 10 days. The incidence of DVT before day 8 was 3.7% (2,500 IU), 1.6% (3,500 IU) and 1.6% (heparin). During the 1-month follow-up period, there was a significantly higher incidence of superficial and/or deep vein thrombosis in the 2,500 IU innohep group (6%) compared with the 3,500 IU group (2.6%) and the heparin group (3.5%). All types of bleeding occurred in approximately 10% of each group during the hospital stay and in 3% from discharge and 1 month onwards, without statistically-significant differences between the three groups.

Venous thromboembolism prophylaxis in high-risk surgery
In a randomised, double-blind study that included 440 patients who underwent total hip replacement surgery, the patients were randomly assigned to groups that received either enoxaparin (4,000 IU once daily) or innohep (4,500 IU once daily) for 15 days with the first injection 12 hours before surgery. The incidence of DVT was 20.1% (44/219) among the enoxaparin patients and 21.7% (48/221) among the innohep patients. Proximal DVT occurred in 10.5% (23/219) of the enoxaparin patients and in 9.5% (21/221) of the innohep patients. Severe bleeding was observed only in connection with the surgical wound (4 patients in the enoxaparin group and 2 in the innohep group). Non-severe bleeding occurred in 21 patients in the enoxaparin group and 13 in the innohep group.

Prophylaxis in haemodialysis patients
An open-label, long-term study that included 1,429 haemodialysis sessions with 52 patients showed no or minimal thrombosis, in 92.8% (1,326/1,429) and a satisfactory anticoagulation effect in 96% (1,370/1,427) of the sessions when innohep was administered as a single bolus dose. The average dose of innohep was 2,139 IU during the first sessions and 2,186 IU during the last sessions of the study. Haemorrhages in the skin or mucous membranes were observed in 27/1,408 (1.9%) of the dialysis sessions.

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. The terminal elimination half-life is approximately 3.7 hours.

innohep undergoes minor metabolisation in the liver through a depolymerisation and is excreted via the kidneys as an unchanged or almost unchanged form.

Special patient populations
Pregnant women
The pharmacokinetic activity of innohep has been studied in pregnant women. Data from sequential pharmacokinetic monitoring of 55 pregnant women indicate that the pharmacokinetic properties do not differ from the pharmacokinetic properties in non-pregnant women.

Renal impairment
innohep has a high, average molecular weight and there is clinical and preclinical evidence of significant non-renal elimination of innohep.
The observed half-life of an intravenous bolus injection that was administered to dialysis patients is shorter than subcutaneous administration to healthy volunteers (approximately 2.5 hours versus approximately 3.7 hours).

In an open-label, randomised, pharmacokinetic comparative study, it was investigated whether any accumulation occurred after repeated daily prophylactic doses of innohep (4,500 IU) or enoxaparin (4,000 IU) over 8 days in elderly patients (> 75 years) with renal impairment (CrCl: 20 to 50 mL/min) and body weight < 65 kg. 55 patients were included in the analysis. The average anti-Xa activity increased significantly in the enoxaparin group (from 0.55 on day 1 to 0.67 on day 8; $p < 0.001$), but not in the innohep group (from 0.44 on day 1 to 0.46 on day 8; $p = 0.296$). No VTE events occurred. Five cases of bleeding, two of which were severe, occurred in the innohep group and four cases of bleeding, one of which was severe, occurred in the enoxaparin group.

In a prospective observational and multi-dose study, bioaccumulation of innohep was evaluated. The study included 28 inpatients who were prescribed innohep for non-surgical thrombosis prophylaxis and with an estimated glomerular filtration rate of ≤ 30 mL/min/1.73 m^2 (mean eGFR at baseline 20 mL/min/1.73 m^2). The patients received 3,500 IU once daily, with a decrease to 2,500 IU once daily if their body weight was < 40 kg, or increasing to 4,500 IU once daily with a BMI ≥ 30 kg/m^2.

The median peak of the anti-Xa levels (range) was measured at the 4th hour on day 2 at 0.07 (0-0.24) IU/mL, 0.11 (0.07-0.25) IU/mL on day 5 and 0.09 (0.07-0.31) IU/mL on day 8. There was no statistically-significant increase in the anti-Xa peak levels over time between day 2 and day 5. The range of variation for the anti-Xa peak levels was comparable with previously published data for surgical patients with normal renal function, receiving 3,500 IU innohep. All anti-Xa peaks remained below 0.4 IU/mL and the anti-Xa trough levels were not detectable, indicating the absence of bioaccumulation. No patient experienced thrombotic complications or severe bleeding events.

Paediatric population
Preliminary data on the use of innohep suggest that younger children including neonates and infants clear innohep 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 acetate trihydrate
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

Prefilled unit dose 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 0.25 ml of solution.
Supplied in packs of 5, 10, 50 and 100 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

PA0046/060/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 December 1997
Date of last renewal: 24 January 2007

10 DATE OF REVISION OF THE TEXT

November 2024