

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

innohep 20,000 IU/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Benzyl alcohol (10 mg/mL), 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 straw coloured sterile 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.

### **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.

This multidose vial formulation of innohep contains 10 mg/ml of the preservative, benzyl alcohol. Therefore, this formulation must not be given to premature babies and neonates due to the risk of gasping syndrome.

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. innohep 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**

#### 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 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 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 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 formulation of innohep contains 10 mg/ml of the preservative, benzyl alcohol. Benzyl alcohol may cause allergic reactions. Benzyl alcohol may cause toxic and anaphylactoid reactions in infants and children up to three years old. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

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 interactions**

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 innohep are 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 innohep and 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. 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.

##### *Excipients*

innohep vials contain benzyl alcohol. As this preservative may cross the placenta and may cause accumulation and toxicity (metabolic acidosis), innohep formulations without benzyl alcohol (syringes) should be used during pregnancy.

##### 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.

##### *Excipients:*

innohep vials contain benzyl alcohol. Due to a risk of accumulation and toxicity (metabolic acidosis), innohep formulations without benzyl alcohol (pre-filled syringes) are the preferred choice during breast-feeding.

##### 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  $\geq 1/10$

Common  $\geq 1/100$  and  $< 1/10$

Uncommon  $\geq 1/1,000$  and  $< 1/100$

Rare  $\geq 1/10,000$  and  $< 1/1,000$

Very rare  $< 1/10,000$

<b>Blood and lymphatic system disorders</b>	
Common $\geq 1/100$ and $< 1/10$	Anaemia (incl. haemoglobin decreased)
Uncommon $\geq 1/1,000$ and $< 1/100$	Thrombocytopenia (type I) (incl. platelet count decreased)
Rare $\geq 1/10,000$ and $< 1/1,000$	Heparin induced thrombocytopenia (type II) Thrombocytosis
<b>Immune system disorders</b>	
Uncommon $\geq 1/1,000$ and $< 1/100$	Hypersensitivity
Rare $\geq 1/10,000$ and $< 1/1,000$	Anaphylactic reaction
<b>Metabolism and nutrition disorders</b>	
Rare $\geq 1/10,000$ and $< 1/1,000$	Hypoaldosteronism associated with hyperkalaemia and metabolic acidosis
<b>Vascular disorders</b>	
Common $\geq 1/100$ and $< 1/10$	Haemorrhage Haematoma
Uncommon $\geq 1/1,000$ and $< 1/100$	Bruising, ecchymosis and purpura
<b>Hepatobiliary disorders</b>	
Uncommon $\geq 1/1,000$ and $< 1/100$	Hepatic enzyme increased (incl. increased transaminases, ALT, AST and GGT)
<b>Skin and subcutaneous tissue disorders</b>	

Uncommon $\geq 1/1,000$ and $< 1/100$	Dermatitis (incl. allergic dermatitis and bullous) Rash Pruritus
Rare $\geq 1/10,000$ and $< 1/1,000$	Toxic skin eruption (including Stevens-Johnson syndrome) Skin necrosis Angioedema Urticaria
<b>Musculoskeletal and connective tissue disorders</b>	
Rare $\geq 1/10,000$ and $< 1/1,000$	Osteoporosis (in connection with long-term treatment)
<b>Reproductive system and breast disorders</b>	
Rare $\geq 1/10,000$ and $< 1/1,000$	Priapism
<b>General disorders and administration site conditions</b>	
Common $\geq 1/100$ 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 HPRC Pharmacovigilance, Website: [www.hpra.ie](http://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

ATC code: B01AB10

innohep is a low molecular weight heparin produced by controlled enzymatic depolymerisation of conventional sodium heparin derived from porcine mucosa.

innohep is an anticoagulant like conventional heparin. It potentiates the inhibition of several activated coagulation factors, especially Factor Xa, its activity being mediated via Antithrombin III.

The biological activity of innohep is standardised against the current International standard for low molecular weight heparins and is expressed in anti-factor Xa international units.

### 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 (E223)

Benzyl alcohol

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**

2 years.

Chemical and physical in use stability has been demonstrated for 28 days at 30°C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 30°C. Other in-use storage times and conditions are the responsibility of the user.

### **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**

Uncoloured Type 1 glass vial, sealed with a chlorobutyl stopper.

Each vial contains 2 ml of solution containing tinzaparin sodium 20,000 IU/ml.

Pack sizes: Packs of 1 and 10 vials.

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**

PA0046/060/003

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

Date of first authorisation: 15 February 1995

Date of last renewal: 14 February 2010

**10 DATE OF REVISION OF THE TEXT**

January 2020