December 2021

Dear Doctor/Pharmacist

Advancing the care of patients with thrombosis

innohep® (tinzaparin sodium):

Out of Stock Notification

LEO Pharma
Cashel Road
Dublin
D12 E923
Ireland

LEO Laboratories Limited T/A
LEO Pharma
Registered in Ireland No. 16885
Registered Office: 285 Cashel Road, Dublin 12

Tel: +353 1 490 8924
Fax: +353 1 490 1606

www.leo-pharma.ie

IE/MAT-53224v.2
December 2021

LEO Pharma is currently experiencing a delay in release of expected stock of innohep® (tinzaparin sodium) 4,500 IU syringe, affecting the IE market.

Product name	**Product Authorisation**
innohep® 4,500 IU in 0.45 ml, solution for injection	PA 46-60-07

There are no safety or quality issues with current stock therefore you may continue to dispense or use any available stock. We will be out of stock during January and mid February 2022.

Alternative presentations

During the period when innohep® 4,500 IU in 0.45ml is out of stock

innohep® 10,000 IU solution for injection [PA 46-60-2], which is a multi-dose vial, may also be considered as an alternative and is available on the Irish market. Please note that this multi-dose vial presentation contains benzyl alcohol, a preservative which should not be used during pregnancy or with infants and children.

Please note that innohep® is licensed only in adults, refer to the SmPC on www.medicines.ie for full prescribing information and precautions on all innohep® presentations.

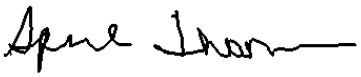
Our aim is to ensure treatment continuity and availability for patients, and we sincerely apologise for any inconvenience this out of stock period may cause you or your patients.

If you require any further information, please do not hesitate to contact our Medical Information team as follows via:

Telephone: +353 1 4908924 or Email: medical-info.ie@leo-pharma.com

Please forward this correspondence to relevant healthcare professionals as you see appropriate.

Yours sincerely,



April Thompson

Medical Affairs Director, LEO Pharma UK/IE

Advancing the care of patients with thrombosis

Reporting of Suspected Adverse Reactions

Adverse events should be reported.

Reporting forms and information can be obtained from: HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

Adverse events should also be reported to Drug Safety at LEO Pharma by calling +353 1 4908924 or e-mail: medical-info.ie@leo-pharma.com

Prescribing Information for innohep® 2,500 IU/3,500 IU/4,500 IU, solution for injection *(fixed dose pre-filled syringes)*, innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection *(variable dose pre-filled syringes)*, innohep® 10,000 IU/ml, solution for injection *(vial)* and innohep® 20,000 IU/ml, solution for injection *(vial)* – *[tinzaparin sodium]*
Please refer to the full Summary of Product Characteristics (SmPC) (www.medicines.ie) before prescribing.
Indications: ***innohep® 2,500 IU/3,500 IU/4,500 IU, solution for injection (fixed dose pre-filled syringes) and innohep® 10,000 IU/ml, solution for injection (vial);*** Prophylaxis of venous thromboembolism (VTE) in adult patients undergoing surgery, particularly orthopaedic, general or oncological surgery. Prophylaxis of VTE 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. ***innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection (variable dose pre-filled syringes) and innohep® 20,000 IU/ml, solution for injection (vial);*** Treatment of venous thrombosis and thromboembolic disease including deep vein thrombosis and pulmonary embolus (PE) 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. **Active ingredient:** Tinzaparin sodium 10,000 anti-Factor Xa IU/ml and tinzaparin sodium 20,000 anti-Factor Xa IU/ml. **Dosage and administration:** ***innohep® 2,500 IU/3,500 IU/4,500 IU, solution for injection (fixed dose pre-filled syringes) and innohep® 10,000 IU/ml, solution for injection (vial);*** Subcutaneous (SC) injection and as indicated for haemodialysis/haemofiltration. *Prophylaxis of thromboembolic events in adults: Surgical patients at moderate risk of thromboembolic events:* 3,500 anti-Xa IU 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 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 once daily in patients at moderate risk of VTE, or 4,500 anti-Xa IU 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. If neuraxial anaesthesia 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 satisfactory response obtained. The usual dose is within 2,000 - 4,500 anti-Xa IU. In 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 dose during haemodialysis/haemofiltration. The plasma anti-Xa level should be approximately 0.5 anti Xa IU/ml one hour after administration. *Paediatric population:* The safety and efficacy of innohep in children below 18 years have not yet been established; no posology recommendations can be made. *Renal impairment:* If renal impairment suspected, assess renal function using a formula based on serum creatinine to estimate creatinine clearance (CrCl) level. Use in patients with a CrCl level <30 ml/min not recommended, as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with CrCl 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. *Elderly:* Use innohep in standard doses. Precaution recommended in elderly patients with 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:* Inspect product visually prior to administration. Do not use if cloudiness or precipitate is observed. The liquid may turn yellow during storage but is still useable. Administer by SC injection when given as prophylaxis of thromboembolic events in adults; this can be done in abdominal skin, 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. For haemodialysis, the dose 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. ***innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection (variable dose pre-filled syringes) and innohep® 20,000 IU/ml, solution for injection (vial);*** Subcutaneous (SC) injection only. *Adults:* 175 anti Xa IU/kg body weight 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 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) contraindicated. If neuraxial anaesthesia planned, discontinue innohep at least 24 hours before 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. *Paediatric population:* The safety and efficacy of innohep in children below 18 years have not yet been established; no posology recommendations can be made. *Renal impairment:* If renal impairment suspected, assess renal function using a formula based on serum creatinine to estimate creatinine clearance (CrCl) level. Use in patients with a CrCl level <30 ml/min not recommended, as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with CrCl 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. 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:* Use innohep in standard doses. Precaution recommended in the treatment of elderly patients with renal impairment. *Method of administration:* Inspect product visually prior to administration. Do not use if cloudiness or precipitate is observed. The liquid may turn yellow by storage but is still suitable. Administer by SC injection; this can be done in abdominal skin, 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. *Syringes only:* 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. **Contraindications:** Hypersensitivity to constituents. Current or history of immune-mediated heparin-induced thrombocytopenia (HIT) - type II. Active major haemorrhage or conditions predisposing to major haemorrhage, 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. **Vial formulations** contains 10 mg/ml benzyl alcohol and must not be given to premature babies and neonates. ***innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection (variable dose pre-filled syringes) and innohep® 20,000 IU/ml, solution for injection (vial);*** Treatment doses (175 IU/kg) contraindicated in patients who receive neuraxial anaesthesia. If neuraxial anaesthesia planned, discontinue innohep at least 24 hours before procedure performed. innohep should not be resumed until at least 4-6 hours after the use of spinal anaesthesia or after catheter has been removed. Monitor patients closely for signs and symptoms of neurological injury. **Precautions and warnings:** *Neuraxial anaesthesia:* Patients undergoing epidural/spinal anaesthesia or spinal puncture: Prophylactic use of heparin may be very rarely associated with epidural/spinal haematoma resulting in prolonged or permanent paralysis. Risk increased by use of epidural/spinal catheter, concomitant use of drugs affecting haemostasis and traumatic/repeated puncture. Extreme vigilance and frequent monitoring required. ***innohep® 2,500 IU/3,500 IU/4,500 IU, solution for injection (fixed dose pre-filled syringes) and innohep® 10,000 IU/ml, solution for injection (vial);*** Minimum delay of 12 hours between last prophylactic dose of innohep and needle/catheter replacement. Do not resume innohep until at least 4 to 6 hours after spinal anaesthesia or catheter removal. *Haemorrhage:* Caution in patients with increased risk of haemorrhage. *Intramuscular (IM) injections:* Do not administer by IM injection; avoid concomitant IM injections due to risk of haematoma. *HIT:* Measure platelet counts before treatment and periodically thereafter (risk of immune-mediated Type II HIT). innohep must be discontinued in patients who develop immune-mediated Type II HIT. Platelet counts will usually normalise within 2 to 4 weeks after withdrawal of innohep. ***innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection (variable dose pre-filled syringes) and innohep® 20,000 IU/ml, solution for injection (vial);*** 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 can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium-sparing drugs, on long-term innohep. Measure plasma potassium in patients at risk before starting therapy; monitor regularly. Heparin-related hyperkalaemia usually reversible upon treatment discontinuation, although other approaches may need to be considered (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance). *Prosthetic heart valves:* Not recommended. No adequate studies therefore no dosage recommendations can be given. *Renal impairment:* Use in patients with a CrCl level <30 ml/min not recommended, as dosage in this population not established. Available evidence demonstrates no accumulation in patients with CrCl levels down to 20 ml/min. When required in these patients, innohep can be used cautiously with anti-Xa monitoring, if the benefit outweighs the risk. Although anti-Xa monitoring remains a poor predictor of haemorrhage risk, it is the most appropriate measure of the pharmacodynamic effects of innohep. *Elderly:* Caution advised as more likely to have reduced renal function. *Interchangeability:* Low molecular weight heparins (LMWHs) should not be used interchangeably. Switching to an alternative LMWH, especially during extended use, must be exercised with particular caution and specific dosing instructions for each proprietary product must be followed. *Excipients warnings:* Contains sodium metabisulfite (E223). Metabisulfites may rarely cause severe hypersensitivity reactions including bronchospasm. Use with caution in patients with asthma. **Vial formulation** contains benzyl alcohol which may cause allergic reactions, toxic and anaphylactoid reactions in infants and children up to 3 years old (see contraindications). High volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of accumulation of toxicity (metabolic acidosis). **Drug interactions:** Anticoagulant effect of innohep may be enhanced by other drugs affecting the coagulation system, such as those inhibiting platelet function, thrombolytic agents, vitamin K antagonists, activated protein C, small molecule anti-Xa and IIa inhibitors. Avoid or carefully monitor such combinations. **Fertility, pregnancy and lactation:** *Pregnancy:* Tinzaparin does not cross the placenta. Can be used during all trimesters of pregnancy if clinically needed. *Excipients warnings:* **Vial formulation** contains benzyl alcohol which may cause accumulation and toxicity (metabolic acidosis). **Avoid use of vial formulation during pregnancy.** *Epidural anaesthesia:* Treatment doses contraindicated due to risk of spinal haematoma. Delay epidural anaesthesia until at least 24 hours after last treatment dose of innohep due to risk of spinal haematoma. Prophylactic doses may be used as long as a minimum delay of 12 hours is allowed between last administration of innohep and needle or catheter placement. *Use in pregnant women with prosthetic heart valves:* Not recommended. *Breast-feeding:* Not known whether tinzaparin excreted into human milk. Although oral absorption of LMWHs is unlikely, risk to the breast-fed child cannot be excluded. In patients at risk, the incidence of VTE is particularly high during the first 6 weeks after child birth. Risk/benefit decision must be made whether to discontinue breast-feeding or to discontinue/abstain from innohep therapy. *Excipients warning:* **Vial formulation** contains 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:* No clinical studies. **Side effects:** *Common:* anaemia (incl. haemoglobin decreased), haemorrhage, haematoma, injection site reactions (incl. injection site haematoma, haemorrhage, pain, pruritus, nodule, erythema and extravasation). *Uncommon:* thrombocytopenia (type I) (incl. platelet count decreased), hypersensitivity, bruising, ecchymosis, purpura, hepatic enzyme increased (incl. increased transaminases, ALT, AST and GGT), dermatitis (incl. allergic dermatitis and bullous dermatitis), rash, pruritus. *Rare:* HIT (type II), thrombocytosis, anaphylactic reaction, hypoaldosteronism associated with hyperkalaemia and metabolic acidosis, toxic skin eruption (incl. Stevens-Johnson syndrome), skin necrosis, angioedema, urticaria, osteoporosis (in connection with long-term treatment), priapism. *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. ***innohep® 8,000 IU in 0.4 ml/10,000 IU in 0.5 ml/12,000 IU in 0.6 ml/14,000 IU in 0.7 ml/16,000 IU in 0.8 ml/18,000 IU in 0.9 ml, solution for injection (variable dose pre-filled syringes) and innohep® 20,000 IU/ml, solution for injection (vial);*** *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 events 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. 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. **Legal category:** Product subject to prescription. **Marketing Authorisation Number and Holder:** ***(syringes)*** innohep® 2,500 IU – PA 46/60/8, innohep® 3,500 IU – PA 46/60/9, innohep® 4,500 IU – PA 46/60/7, innohep® 8,000 IU in 0.4 ml – PA 46/60/12, innohep® 10,000 IU in 0.5 ml – PA 46/60/10, innohep® 12,000 IU in 0.6 ml – PA 46/60/13, innohep® 14,000 IU in 0.7 ml – PA 46/60/11, innohep® 16,000 IU in 0.8 ml – PA 46/60/14, innohep® 18,000 IU in 0.9 ml – PA 46/60/4; ***(vial)*** innohep® 10,000 IU/ml - PA 46/60/2, innohep® 20,000 IU/ml – PA 46/60/3. LEO Laboratories Limited, Cashel Road, Dublin 12, Ireland.
Last revised: February 2020 REF-05030 (3)
Further information can be found in the Summary of Product Characteristics or from: LEO Pharma, Cashel Road, Dublin 12, Ireland. email: medical-info.ie@leo-pharma.com

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.

Adverse events should also be reported to Drug Safety at LEO Pharma by calling +353 1 4908924 or e-mail medical-info.ie@leo-pharma.com

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