— we help people achieve healthy skin

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Important Product Information Update for Healthcare Professionals (HCP)

Update to the Prescribing Information for innohep® 20,000 IU/ml (tinzaparin sodium) Vial and Syringes

	Product / strength	Product authorisation number	Active substance
20,000 IU/ml Vial (for SC injection)	innohep® 20,000 IU/ml	PA 0046/060/003	tinzaparin sodium
20,000 IU/ml Syringes (for SC injection)	innohep® 8,000 IU in 0.4 ml	PA 0046/060/012	
	innohep® 10,000 IU in 0.5 ml	PA 0046/060/010	
	innohep® 12,000 IU in 0.6 ml	PA 0046/060/013	
	innohep® 14,000 IU in 0.7 ml	PA 0046/060/011	
	innohep® 16,000 IU in 0.8 ml	PA 0046/060/014	
	innohep® 18,000 IU in 0.9 ml	PA 0046/060/004	

Dear Healthcare Professional,

LEO Pharma would like to inform you of the following:

The Summary of Product Characteristics (SmPCs) for innohep® 20,000 IU/ml Vial and Syringes have been updated following a European Union (EU) harmonisation work-sharing procedure. This update was as a result of a review by the EU Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) in 2014, when significant differences in section 4.1 (Therapeutic indications) and section 4.2 (Posology and Method of Administration) of the SmPCs across the EU were noted.

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It was therefore agreed that section 4.1 and section 4.2 would be aligned across the EU, including consequential changes to section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects). It was also agreed at that time for the SmPCs to be revised to include the data from the CATCH trial as part of this work-sharing procedure.

Please note that this communication only highlights the changes to the product information in relation to the EU harmonisation procedure. HCPs should refer to the updated SmPCs and PILs for full prescribing information, which are available at www.hpra.ie and www.medicines.ie.

Summary of significant changes to the SmPCs

Section 4.1, Therapeutic indications

The following wording (in italics) has been added to the existing indication of '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.

Section 4.2, Posology and Method of Administration

The following wording has been added to the posology section:

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.

The renal impairment sub-section has been amended to the following:

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.

The Method of Administration sub-section has been amended to:

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.

***Following wording and table added for 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.

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*

Section 4.4, Special warnings and precautions for use

The sub-section 'Heparin-induced thrombocytopenia' includes the following additional wording:

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.

The sub-section 'Renal impairment' has been amended to:

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.

A new sub-section on 'Interchangeability' has been added:

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.

Section 4.8, Undesirable effects

A new sub-section on patients with cancer on extended treatment has been added:

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.

Please ensure that all relevant staff are made aware of the content of this letter and that the information is communicated to all relevant HCPs within your hospital, as appropriate.

The communication of this information has been agreed with the Health Products Regulatory Authority (HPRA).

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 to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - 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 LEO Pharma by calling +353 1 4908924 or e-mail medical-info.ie@leo-pharma.com. If you have any questions, please contact LEO Medical Information by calling +353 1 4908924 or e-mail medical-info.ie@leo-pharma.com.

Yours sincerely

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