Heparin LEO®

1. NAME OF THE MEDICINAL PRODUCT

Heparin LEO®
Heparin sodium

Carefully read this insert before administering this product. It contains information about your treatment. If you have any doubt or you are not sure about something, please ask your physician or Pharmacist.
Keep this insert as you might need to read it again.
Verify this product fully corresponds to the one prescribed by your physician.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 1,000 IU/ml
Pack sizes: 5 ml x 5 and 5 ml x 50
Excipients, which the clinician should be aware of:
Benzyl alcohol, methyl parahydroxybenzoate and propyl parahydroxybenzoate

Heparin sodium 5,000 IU/ml
Pack sizes: 5 ml x 5 and 5 ml x 50
Excipients, which the clinician should be aware of:
Benzyl alcohol, methyl parahydroxybenzoate and propyl parahydroxybenzoate

All excipients are listed under section 6.1

Not all pack sizes and strengths may be marketed

Sale under prescription

3. PHARMACEUTICAL FORM

Solution for injection

Vials with clear, colourless or yellow liquid, free of turbidity and visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Heparin is indicated for prophylaxis and treatment of venous thrombosis and pulmonary embolism; in the treatment of myocardial infarction and arterial embolism; for prevention of clotting in arterial and heart surgery and for prevention of cerebral thrombosis. Heparin may also be used as an anticoagulant in blood transfusions, extra-corporal circulation, dialysis procedures, and for laboratory purposes.

4.2 Posology and method of administration

Heparin is usually administered by intravenous or subcutaneous injection. The intramuscular route cannot be recommended because of the high incidence of haematoma.
The increase in clotting time provided by heparin becomes apparent immediately after administration and lasts for 4 to 6 hours after intravenous injection and for about eight hours after subcutaneous injection.

Dosage
Haemodialysis: 7,500–12,500 IU is normally required per dialysis. Intravenous administration: 5,000–10,000 IU every four hours either by bolus injection or continuous infusion in Sodium Chloride Injection or Dextrose Injection. However, the dose should be monitored with coagulation tests performed just before each administration and varied according to individual response. The clotting time should be 2–3 times the control value.
Subcutaneous administration (Therapeutic dosage): Subcutaneous administration of 10,000 IU may be given every 8 hours after an initial intravenous bolus injection of 5,000 IU.
Low-dose heparin prophylaxis: 5,000 IU s.c. should be given two to six hours pre-operatively and every 8 –12 hours post-operatively for 10–14 days, or until the patient is mobile, whichever is the longer.
Myocardial infarction: 5,000 IU s.c. every twelve hours beginning during the twelve hours following the first sign of myocardial infarction.
Open heart surgery: Operations of less than two hours, 120 IU/kg/hour. For operations of longer duration, one and a half times this dose should be given. For each 450 ml of blood used, 2,000 IU are needed.
Treatment periods vary from 10–14 days in perioperative prophylaxis to as much as six weeks in the treatment of established thrombosis.
It is anticipated that heparin will have disappeared from the blood-stream 4 hours after intravenous injection of 5,000 IU and 6–8 hours after 10,000 IU and 15,000 IU of i.v. heparin, respectively.
In situations needing large amounts of heparin, as in cardio-pulmonary bypass, preservative-free heparin should be used. If this is unavailable and preserved heparin has to be used, then the most concentrated heparin solution should be chosen to minimise the quantity of preservative administered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

It is also contraindicated when suitable blood coagulation tests – e.g. the whole-blood clotting time, partial thromboplastin time, – cannot be performed at the required intervals. There is usually no need to monitor the effect of low-dose heparin in patients with normal coagulation parameters. The drug is contraindicated during any uncontrolled active bleeding state (see section 4.4).

Current or previous immune-mediated heparin-induced thrombocytopenia (type II) (see section 4.4).

Active major haemorrhage and risk factors for major haemorrhage. Major haemorrhage is defined as fulfilling one of these four criteria:
1) Fatal bleeding. 2) Bleeding in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome. 3) Bleeding which induces a decrease in the haemoglobin

level of 20g/L (1.24mmol/L) or more. 4) Bleeding leading to transfusion of two or more units of whole blood or red blood cells.

Septic endocarditis.

Heparin LEO® is contra-indicated in locoregional anesthesia in patients receiving heparin for treatment rather than for prophylaxis. Heparin LEO® is also contraindicated for insertion of epidural catheter in patients receiving treatment doses. Removal or manipulation of an epidural catheter should only be done, when the benefit outweighs the risk (see section 4.4).

Heparin LEO® contains 10 mg/ml of the preservative benzyl alcohol. This must not be given to premature babies or neonates due to the risk of gasping syndrome.

4.4 Special warnings and precautions for use

Caution is advised when administering Heparin LEO® to patients at risk of haemorrhage.

The combination with medicinal products affecting platelet function or the coagulation system should be avoided or carefully monitored (see section 4.5).

In patients undergoing peridural or spinal anaesthesia or spinal puncture, the prophylactic use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. The risk is increased by the use of a peridural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants, and by traumatic or repeated puncture.

In decision-making on the interval between the last administration of heparin at prophylactic doses (≤15.000 IU/day) and the placement or removal of a peridural or spinal catheter, the product characteristics and the patient profile should be taken into account. Placement or removal of a peridural or spinal catheter should not be allowed until 4–6 hours after the last heparin administration and a subsequent dose should not take place before at least 1 hour post procedure. For treatment doses (>15.000 IU/day), placement or removal of a peridural or spinal catheter should not be allowed until 4-6 hours after last intravenous heparin administration or 8-12 hours after last subcutaneous heparin administration. Re-administration should be delayed until the surgical procedure is completed or at least 1 hour post procedure.

Should a physician decide to administer anticoagulation in the context of peridural or 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) and bowel or bladder dysfunction. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these. If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated. Heparin 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.

Because of the risk of immune-mediated heparin-induced thrombocytopenia (type II), platelet count should be measured prior to treatment and periodically thereafter. Heparin LEO® 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.

Low molecular weight heparin should not be used as an alternative to heparin in case of heparin-induced thrombocytopenia (type II).

Heparin products can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see section 4.8). Risk factors include diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma level of potassium at pre-treatment, concomitant therapy with drugs that may elevate plasma potassium and long-term use of heparin (see section 4.5).

In patients at risk, potassium levels should be measured before starting Heparin LEO® and monitored regularly thereafter. Heparin-related hyperkalaemia is usually reversible upon treatment discontinuation, though other approaches may need to be considered if heparin treatment is considered lifesaving (e.g. decreasing potassium intake, discontinuing other drugs that may affect potassium balance).

Heparin therapy should be given with caution to patients about to undergo surgery, and those with impaired renal or hepatic function. If oral anticoagulants are started, heparin should be continued in slightly decreasing doses for another 4–5 days until the oral drug has attained full prothrombin depressing activity.
Heparin should be used with caution in any patient with a history of allergy. Before a therapeutic dose is given to such a patient, a trial dose of 1,000 units may be advisable.

Heparin may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least five hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

Elderly women have a greater tendency to bleed and it may be necessary to reduce the dose according to coagulation tests, but dosage alterations are unlikely for prophylaxis.

Heparin LEO® contains benzyl alcohol, methyl parahydroxybenzoate and propyl parahydroxybenzoate and sodium as excipients.
Methyl parahydroxybenzoate and propyl parehydroxybenzoate may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see section 4.3).

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml vial, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medical products and other forms of interaction

The anticoagulant effect of Heparin LEO® may be enhanced by concomitant administration of other drugs affecting the coagulation system, such as those inhibiting platelet function (e.g. acetylsalicylic acid, other non-steroidal anti-inflammatory drugs

(NSAIDs) and selective serotonin reuptake inhibitors (SSRIs)), thrombolytic agents, vitamin K antagonists, activated protein C and direct factor Xa and IIa inhibitors. Such combinations should be avoided or carefully monitored (see section 4.4).

Drugs (such as dextran) that interfere with platelet-aggregation reactions may induce bleeding and should be used with caution in patients receiving heparin. It may be necessary to increase doses of heparin in the febrile state. Nicotine may partially counteract the anticoagulant action of heparin sodium

4.6 Pregnancy and lactation

Fertility
There are no clinical studies with heparin regarding fertility.

Pregnancy
Anticoagulant treatment of pregnant women requires specialist involvement.

Heparin does not cross the placenta and can be used during all trimesters of pregnancy if clinically needed.

Caution should be exercised in relation to the risk of haemorrhage, especially during delivery and epidural anaesthesia (see sections 4.3 and 4.4).

Due to the risk of spinal haematoma, treatment doses of heparin 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 4-6 hours after intravenous administration of the last treatment dose of heparin, and 8-12 hours after subcutaneous administration of the last treatment dose of heparin.
However, prophylactic doses may be used as long as a minimum delay of 4-6 hours is allowed between the last administration of heparin and the needle or catheter placement (see section 4.4).

Heparin LEO® contains benzyl alcohol. As this preservative may cross the placenta, Heparin sodium formulations without benzyl alcohol should be used during pregnancy.
Breastfeeding
Heparin is not excreted in human milk and can be used during breastfeeding.

4.7 Effect on ability to drive and use machinery

Heparin LEO® has no or negligible influence on the ability to drive or use machines.

4.8 Adverse reactions

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and spontaneous reporting.

The most frequently reported adverse reactions are haemorrhage and erythema.

Haemorrhage may present in any organ and have different degrees of severity (see section 4.4). Complications may occur particularly when high doses are administered. Although major haemorrhages are uncommon, death or permanent disability have been reported in some cases.

Immune-mediated heparin-induced thrombocytopenia (type II) is an uncommon but well-known adverse reaction in connection with heparin therapy. 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. Heparin must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia (type II) (see section 4.4).

In rare cases, heparin may cause hyperkalaemia due to hypoaldosteronism. Patients at risk include those with diabetes mellitus or renal impairment (see section 4.4).

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	
Uncommon: (≥1/1,000 and <1/100)	Thrombocytopenia, including non-immune heparin associated thrombocytopenia (type I).
Immune system disorders	
Uncommon: (≥1/1,000 and <1/100)	Anaphylactic reaction Heparin-induced thrombocytopenia (type II) Hypersensitivity.
Metabolism and nutrition disorders	
Uncommon: (≥1/1,000 and <1/100)	Hyperkalaemia
Vascular disorders	
Common: (≥1/100 and <1/10)	Haemorrhage Haematoma
Skin and subcutaneous tissue disorders	
Common: (≥1/100 and <1/10)	Erythema
Uncommon: (≥1/1,000 and <1/100)	Skin necrosis Rash* Urticaria Pruritus *Various types of rashes such as erythematous, generalised, macular, maculo-papular, papular and pruritic have been reported
Musculoskeletal and connective tissue disorders	
Uncommon: (≥1/1,000 and <1/100)	Osteoporosis (in connection with long-term treatment).
Reproductive system and breast disorders	
Uncommon: (≥1/1,000 and <1/100)	Priapism.
General disorders and administration site conditions	
Uncommon: (≥1/1,000 and <1/100)	Injection site reaction.
Investigations	
Common: (≥1/100 and <1/10)	Increased transaminases.

Uncommon: (≥1/1,000 and <1/100)	Activated partial thromboplastin time prolonged beyond therapeutic range.

Paediatric population
The observed safety profile is similar in children and adults.

4.9 Overdose

Haemorrhage is the main complication of overdose.
As heparin is eliminated quickly, a discontinuation of treatment is sufficient in case of minor haemorrhages.
Serious bleeding may require the administration of the antidote protamine sulphate.
Patients should be carefully monitored.

5 PHARMACOLOGICAL PROPERTIES

Therapeutic classification: B 01 AB 01 – Antithrombotic – Heparin group

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in vivo and in vitro. Following administration of full therapeutic doses of heparin the wholeblood clotting time, the thrombin time and the one-stage prothrombin time are prolonged. The prolongation of clotting time is proportional to the dose administered. Whereas with therapeutic doses, the bleeding time is usually unaffected. In most cases the clotting time is not measurably affected by low doses of heparin.
Heparin has immediate effect when administered intravenously. After subcutaneous injection, the maximal coagulation prevention effect in the plasma is after 4-6 hours and bioavailability is approx. 30%. The elimination half-life is 60-90 minutes, longest with higher doses. Heparin metabolises in the liver and is excreted through the urine.

Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin lll (heparin cofactor) can prevent the development of a hypercoagulable state by inactivating activated Factor X, preventing the conversion of prothrombin to thrombin (the principle of low dose prohylaxis). Once a hypercoagulable state exists, larger amounts of heparin in combination with antithrombin lll can inhibit the coagulation process by inactivating thrombin and earlier clotting intermediates, thus preventing the conversion of fibrinogen to fibrin (the principle of full dose therapy). Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.
Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.
In addition to the anticoagulant properties, heparin also has some lipaemia clearing effect, which may be utilized in the treatment and prevention of atherosclerosis and fat embolism.

With overdosing, Heparin can increase the tendency to bleed, due to the pharmacodynamic effect, but otherwise it is only very slightly toxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium citrate, benzyl alcohol, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), hydrochloric acid, water for injection.

6.2 Incompatibilities

Heparin should not be added to infusion fluids containing aminoglycosides, tetracyclines, erythromycin, vancomycin, polymyxin, methicillin, hydrocortisone succinate, promazine chloride and promethazine chloride.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

In-use period: 28 days when stored below 30°C.

Keep out of the reach of children

7. MANUFACTURER

LEO Pharma A/S, 55, Industriparken, DK-2750 Ballerup, Denmark

This leaflet was last revised in November 2016