SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Heparin (Mucous) Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Heparin Sodium 1,000 IU.
Excipients with known effect:
Benzyl alcohol
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium chloride

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear, colourless to yellowish liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of thrombo-embolic disorders such as deep vein thrombosis, acute arterial embolism or thrombosis, thrombophlebitis, pulmonary embolism and fat embolism.

For prophylaxis against deep vein thrombosis and thrombo-embolic events in susceptible patients.

For the prevention of clotting in the extracorporeal circuit during haemodialysis.

4.2 Posology and method of administration

Posology

For the treatment or prevention of thrombo-embolic disorders:

Treatment Dosage:

Intravenous administration

5,000-10,000 IU every 4 hours or 500 IU/kg bodyweight daily as a continuous infusion in sodium chloride injection or dextrose injection. Doses should be individually adjusted according to coagulation tests.

Subcutaneous administration

The initial dose is 250 IU/kg bodyweight. Further doses should be given every 12 hours and individually adjusted according to coagulation tests.

Dosage adjustment

It is recommended that dosages be adjusted to maintain a thrombin clotting time, whole blood clotting time or activated partial thromboplastin time 1.5 to 2 times that of control on blood withdrawn 4 - 6 hours after the first injection or commencement of infusion and at similar intervals until the patient is stabilised.

Prophylactic Dosage:

Administration is by subcutaneous injection.

Patients undergoing major elective surgery:

5,000 IU should be given 2 hours pre-operatively and then every 8 - 12 hours post-operatively for 10 - 14 days or until the patient is ambulant, whichever is the longer.

Following myocardial infarction:

5,000 IU should be given twice daily for 10 days or until the patient is mobile.

Other patients:

5,000 IU should be given every 8-12 hours.

These standard prophylactic regimens do not require routine control.

Dosage in Children

Treatment Dosage:

Standard treatment dosages should be given initially. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

Dosage in the Elderly

Treatment Dosage:

Lower treatment dosages may be required. However, standard treatment dosages should be given initially and then subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

Prophylactic Dosage:

Dosage alterations are unnecessary for prophylaxis in the elderly.

Pregnancy

This heparin formulation contains the preservative benzyl alcohol. As benzyl alcohol may cross the placenta the use of this formulation should be avoided in pregnancy. If use is considered essential, the dosage recommendations given in this section should be followed.

Treatment Dosage:

Standard treatment dosages should be given initially by continuous intravenous infusion, or every 12 hours by subcutaneous injection. Intermittent intravenous injections are not advised. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

Prophylactic Dosage:

It is recommended that plasma heparin levels be maintained below 0.4 IU/ml as determined by specific anti-Xa assay. A suggested dosage is 5,000 IU every 12 hours in early pregnancy increasing to 10,000 IU every 12 hours in the last trimester. The dosage should be reduced during labour and the standard prophylactic dosage is suitable in the puerperium.

For the prevention of clotting during haemodialysis:

An initial bolus dose should be given, followed by a continuous intravenous infusion.

Adults:

Initially: 1,000 - 5,000 IU.

Maintenance: 1,000 - 2,000 IU per hour, adjusted to maintain clotting time > 40 minutes.

Method of administration

For intravenous or subcutaneous injection.

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 and risk factors for major haemorrhage.

Generalised or local haemorrhagic tendency, including uncontrolled severe hypertension, severe liver insufficiency, active peptic ulcer, intracranial haemorrhage or injuries and operations on the central nervous system, eyes and ears, and in women with abortus imminens. This list is not exhaustive.

Septic endocarditis.

In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated because the use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. Furthermore, in patients receiving treatment doses of heparin, insertion of epidural catheter is contraindicated. Removal or manipulation of an epidural catheter should only be done when the benefit outweighs the risk (see sections 4.4 and 4.6).

Heparin 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 to patients at risk of haemorrhage (see section 4.3).

Heparin should be used with caution in patients with hypersensitivity to low molecular weight heparin.

Care should be taken when heparin is administered to patients with increased risk of bleeding complications, hypertension, renal or hepatic insufficiency. This list is not exhaustive.

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 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 anti-coagulation 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 and bowel or bladder dysfunction. 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 before the start of treatment and periodically thereafter. Heparin 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 induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis can occur up to several weeks after discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

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 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 and monitored regularly thereafter, particularly if treatment is prolonged beyond about 7 days. 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).

Excipients

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

Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol can lead to adverse reactions and death in infants (gasping syndrome) and must not be used for infants younger than 4 weeks of age (see section 4.3). It is not known at which amount benzyl alcohol is toxic. Due to risk of accumulation of benzyl alcohol, this medicine should not be used for more than one week in children up to 3 years old.

Extra caution is advised if high doses of benzyl alcohol are used, especially in patients with reduced liver- and kidney function due to risk of accumulation and toxicity (metabolic acidosis). High doses may only be administered if necessary.

Heparin contains 4.1 mg sodium/ml which is less than 1 mmol sodium (23 mg), that is to say essentially ‘sodium-free’ for doses up to 5 ml (corresponding to 5,000 IU heparin sodium).

Heparin contains 41 mg sodium per 10 ml vial. This corresponds to 2.1 % of the WHO recommended maximum daily intake of 2 g for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

The anticoagulant effect of heparin 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, dextrans, activated protein C and direct thrombin inhibitors. Such combinations should be avoided, or carefully monitored (see section 4.4).

Combined use with ACE inhibitors or angiotensin II antagonists may increase the risk of hyperkalaemia; however, this interaction has not been recorded for Heparin LEO.

Use of glyceryl trinitrate infusion may reduce the anticoagulant effect of heparin.

4.6 Fertility, pregnancy and lactation

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.

The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstance.

Reduced bone density has been reported with prolonged heparin treatment during pregnancy.

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 contains benzyl alcohol which may cause accumulation and toxicity (metabolic acidosis). This preservative may cross the placenta.

Breast-feeding

Heparin is not excreted in human milk and can be used during breast-feeding. Heparin contains benzyl alcohol which may cause accumulation and toxicity (metabolic acidosis).

Fertility

There are no clinical studies with heparin regarding fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on a pooled analysis: pooling data together from clinical studies and also a review of data from 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)	Transaminases increased
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.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Heparin group, ATC code: B01AB01

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood *in-vivo* and *in-vitro*. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X.

5.2. Pharmacokinetic Properties

The increase in clotting time provided by heparin becomes apparent immediately after administration and lasts for four to six hours after intravenous injection and for about eight hours after subcutaneous injection.

5.3. Preclinical Safety Data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Sodium citrate

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections

6.2. Incompatibilities

Heparin has been reported to be incompatible in aqueous solution with certain substances, e.g. some antibiotics, hydrocortisone, phenothiazines, narcotic analgesics and some antihistamines.

6.3 Shelf life

3 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

5 x 5 ml vials, 10 x 5 ml vials, 50 x 5 ml vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 0043/0041R.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 December 1975
Date of latest renewal: 15 May 2001

10 DATE OF REVISION OF THE TEXT

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