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Directions for Use
B. Braun Melsungen AG · 34209 Melsungen, Germany

Heparin Sodium Injection 5000 I.U./ml

Composition
1 ml of solution for injection contains
Heparin Sodium (porcine mucosa) according to WHO standard 5,000 I.U.

1 vial (5 ml) of solution for injection contains
Heparin Sodium 25,000 I.U.

Excipients:
Benzyl alcohol (antimicrobial preservative; 10 mg/ml), sodium chloride, water for injections

Pharmaceutical form
Solution for injection
Clear, colourless or faintly straw-coloured aqueous solution

Pharmaco-therapeutic group
Anti-thrombotic agents, heparin group, ATC code B01A B01.

Indications
- Prophylaxis of thrombo-embolism;
- Use as anticoagulant in the therapy of acute venous and arterial thrombo-embolism (including early treatment of myocardial infarction and unstable angina pectoris);
- Prevention of blood clotting during extracorporeal circulation (heart-lung machine, haemodialysis)

Contraindications
Heparin Sodium Injection 5000 I.U./ml must not be used in the following conditions:
- Hypersensitivity to heparin or to any of the excipients of Heparin Sodium Injection 5000 I.U./ml
- Heparin-induced thrombocytopenia (type II) either known from the patient's history or being suspected on grounds of clinical observations such as occurrence of thrombocytopenia or new arterial and/or venous thrombo-embolic complications during therapy
- Diseases associated with haemorrhagic diathesis, such as:
  - coagulopathies
  - thrombocytopenia
  - severe diseases of liver, kidneys, and pancreas
- Diseases where there is a suspicion of vascular damage, e.g.
  - ulcers in the gastro-intestinal tract
  - hypertension with a diastolic blood pressure higher than 105 mm Hg
  - intracranial haemorrhage
  - injuries or surgical procedures on the central nervous system
  - cerebral arterial aneurysm
  - retinopathies, bleeding into the vitreum
  - ophthalmic surgical procedures
  - infectious endocarditis
- Imminent abortion
- Spinal or epidural anaesthesia, lumbar puncture
- Organ lesions associated with haemorrhagic diathesis

Because Heparin Sodium Injection 5000 I.U./ml contains benzyl alcohol, its use is contra-indicated in newborns, esp. in immature pre-term neonates.

Special warnings
Administration of Heparin Sodium Injection 5000 I.U./ml should normally be avoided in the following conditions, unless their expected benefits clearly outweigh possible risks:
- Suspected malignant tumour with risk of bleeding
- Nephro- and ureterolithiasis
- Chronic alcohol abuse.

Especially careful medical monitoring is required:
- during pregnancy, esp. if heparin is to be administered over prolonged periods,
- in elderly patients, especially elderly women,
- during medication with fibrinolytics, oral anticoagulants, drugs inhibiting platelet aggregation, such as acetylsalicylic acid, ticlopidin, clopidogrel, and/or glycoprotein- IIb/IIIa receptor blockers,
- in patients receiving medicaments that raise the serum potassium level.

In general, serum potassium levels should be monitored in patients at risk of hyperkalaemia (e.g. due to diabetes mellitus, impaired renal function, or medicinal products that raise the serum potassium level).
During therapy with heparin, i.m. injections must be avoided because of the risk of haematoma.
If thrombo-embolic complications occur during therapy with heparin, type II heparin-induced thrombocytopenia must be considered and platelet count should be performed.
If heparin is administered to infants, children and patients with hepatic or renal failure, close monitoring including checks of the coagulation status is mandatory. This also applies to the use of heparin for prophylaxis of thrombo-embolism ("low-dose" therapy).
Patients under heparin therapy (more than 22,500 I.U./day) should not be exposed to the risk of injuries.
Heparin may lead to an increase and prolongation of menorrhagia. In case of unusual strong or acyclic uterine bleeding, any organic disease requiring specific treatment should be excluded by a supplementary gynaecological examination.

Special warnings/precautions regarding excipients
Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Precautions for use
Heparin therapy must always be accompanied by regular controls of aPTT and platelet counts.
Prior to administering heparin, the partial thromboplastin time and thrombin time should be determined. Their values should be within the normal range.

In order to detect the occurrence of a type II heparin-induced thrombocytopenia as early as possible, platelet counts should be performed
- before the beginning of the therapy with heparin,
- on the 1st day of therapy,
- every 3rd or 4th day during the first three weeks of therapy, and
- at the end of the therapy.

Heparin may cause various laboratory tests to yield incorrect results, such as erythrocyte sedimentation rate, erythrocyte resistance and complement binding tests.
Heparin may affect the prothrombin time; this should be considered when determining the dosage of coumarin derivatives.

Influence of heparin on laboratory tests:
Heparin may cause various laboratory tests to yield incorrect results, such as erythrocyte sedimentation rate, erythrocyte resistance and complement binding tests.
Under heparin therapy thyroid function tests may yield incorrect results, e. g. falsely high values of T_3 and T_4 levels.

Interactions with other medicinal products and other forms of interaction
Other medicinal products
Enhancement of the heparin effect
Clinically significant enhancement of the heparin effect possibly associated with an increased tendency to bleeding may be brought about by:
- platelet aggregation inhibitors such as acetylsalicylic acid, ticlopidin, clopidogrel, dipyridamol at high-doses,
- fibrinolytics,
- other anticoagulants (coumarin derivatives),
- non-steroidal anti-inflammatory drugs (phenylbutazone, indometacine, sulfinpyrazone),
- glycoprotein-IIb/IIIa receptor blockers,
- high-dose penicillin,
- cytostatic drugs, except doxorubicin
- dextrans

Weakening of the heparin effect
The heparin effect may be weakened by
- *doxorubicin*
- *intravenous glyceryl trinitrate (nitro-glycerine)*

After discontinuation of glyceryl trinitrate the aPTT may rise suddenly. If heparin is administered during nitro-glycerine infusion, close monitoring of the aPTT and adjustment of the heparin dose are necessary.

Inhibition of the heparin effect
The effect of heparin may be inhibited by:
- *Ascorbic acid,*
- *antihistamines,*
- *digitalis (cardiac glycosides),*
- *tetracyclins,*

Influence of heparin on the effect of other drug substances:
- *Other drug substances being bound to plasma proteins (e.g. propranolol):*

Heparin may displace these from protein binding, leading to an enhancement of their effect.
- *Drugs that lead to an increase of the serum potassium level:*

should only be administered together with heparin under careful monitoring.
- *Alkaline drug substances (tricyclic psychotropic agents, antihistamines, or quinine):*

Heparin forms salts with these, leading to mutual weakening of their effects.

Other interactions
- *Nicotine abuse:*

Inhibition of the heparin effect is possible.

Incompatibilities
Heparin solutions should not be mixed with other drugs in a syringe or in an infusion solution because of possible physico-chemical incompatibilities.

Fertility, pregnancy and lactation
Pregnancy
Heparin does not cross the placental barrier. Until now there are no reports indicating development of foetal malformations due to heparin administered during pregnancy, nor are there findings from animal experiments indicating embryotoxic or foetotoxic effects of heparin.
An increased risk of accidental abortions and stillbirths, however, has been reported.
During pregnancy, complications resulting from underlying illness and/or treatment cannot be excluded.
Daily administration of high heparin doses over more than 3 months may increase the risk of osteoporosis in pregnant women. Continuous administration of high doses of heparin should therefore not exceed 3 months.
Epidural anaesthesia must not be performed in obstetrics in pregnant women receiving anticoagulants.
Anticoagulation therapy is contraindicated in conditions characterised by an increased tendency to bleeding, such as imminent abortion (see also section '**Contraindications**').

Lactation
Heparin is not secreted into breast milk. Daily administration of high heparin doses over more than 3 months may increase the risk of osteoporosis in breast-feeding women.

Fertility
No risks are known

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.

Dosage
Determine the heparin dose individually for each patient.
The dosage depends on the actual values of blood coagulation parameters (see section 'special warnings and precautions for use'), type and course of the disease, the patient's response to therapy, type and severity of adverse reactions, as well as the patient's age and body weight (BW). Varying sensitivity to heparin as well as a changed heparin tolerance pattern during therapy must be considered.

Recommended dosages
1) Prophylaxis of thrombo-embolism
For prophylaxis of thrombo-embolism subcutaneous injection is recommended.
General dosage recommendations are as follows:
Pre- and postoperative prophylaxis of thrombo-embolism:
Preoperative:
5 000 to 7 500 I.U. are injected subcutaneously 2 hours prior to beginning of operation.

Postoperative:
Depending on the risk of thrombosis, usually 5 000 I.U. are injected subcutaneously every 8 to 12 hours or 7 500 I.U. every 12 hours, until the patient can be mobilised or until vitamin K antagonists are sufficiently effective. For adjustment of the dosage, determinations of the coagulation status may be required.

Prophylaxis of thrombo-embolism in non-surgical medicine:
(e. g. in patients confined to bed over prolonged periods, patients particularly at risk of thrombosis or suffering from diseases with risk of thrombosis):
Depending on the risk of thrombosis, usually 5 000 I.U. are injected subcutaneously every 8 to 12 hours or 7 500 I.U. every 12 hours.

The dosage should be adjusted according to the individual risk of thrombosis and the activity of the patient's coagulation system; it should be determined according to the values of the patient's coagulation status.

2) In treatment of acute venous and arterial thrombo-embolism
In the presence of clots in blood vessels continuous intravenous administration is recommended.

Adults:
Initially, usually 5 000 I.U. are injected intravenously as bolus, followed by continuous infusion of 1 000 I.U./h using an infusion pump.

Children:
Initially 50 I.U./kg body weight, subsequently 20 I.U./kg kg body weight /h
If continuous intravenous infusion cannot be performed, heparin may be administered by subcutaneous injection, the daily dose being divided into 2 – 3 injections (e.g. 10 000 I.U. – 12 500 I.U. every 12 hours) with close monitoring of the therapeutic effect.
As a rule, the therapy is controlled and doses are adjusted according to the values of the activated partial thromboplastin time (aPTT), which should be 1.5 to 2.5 times the reference value. During continuous infusion, it is recommended to determine the aPTT 1 – 2 hours, 6 hours, 12 hours, and 24 hours after start of the therapy. During subcutaneous administration determinations should be performed 6 hours after administration of the second dose.

Specific dosage recommendations are given as follows:
Treatment of venous thrombo-embolism:
Initially, 5 000 I.U. are injected as bolus intravenously, followed by continuous infusion of 1 000 I.U./h.
The dosage should be adjusted according to the aPTT which should be 1.5 to 2.5 times the reference value. These values should be reached within the first 24 hours of therapy.
Treatment should be continued for at least 4 days or until oral anticoagulation is sufficiently effective.

Use in therapy of unstable angina pectoris or non-Q wave myocardial infarction:
As a rule, initially 5 000 I.U. are injected intravenously as bolus, followed by continuous infusion of 1 000 I.U./h.

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The dose is adjusted according to the values of the aPTT which should be 1.5 to 2.5 times the reference value.
Heparin should be administered over not less than 48 hours.

Adjunct therapy during thrombolysis with fibrin-specific thrombolytic agents (e.g. r-tPA) for therapy of acute myocardial infarction:
Initially, 5 000 I.U. are injected intravenously as bolus, followed by continuous infusion of 1 000 I.U./h.
The dose is adjusted according to the values of the aPTT which should be 1.5 to 2.5 times the reference value.
Heparin should be administered over not less than 48 hours.

Adjunct therapy during thrombolysis with non-fibrin-specific thrombolytic agents (e.g. streptokinase):
When non-fibrin-specific thrombolytic agents are used, alternatively 12 500 I.U. of heparin may be administered subcutaneously every 12 hours, the first dose being given 4 hours after start of thrombolysis.
The exact heparin dose depends on the thrombolytic drug used; the instructions given for the thombolytic drug must be followed. In any case, careful control of the coagulation status is indispensable.

3) Anticoagulation during therapy or surgical procedures using extra-corporeal circulation
Heart-lung machine:
The dosage must be determined individually, depending on the type of heart-lung machine and the duration of the operation.

Haemodialysis:
The dosage must be determined individually, depending on the patient's coagulation status and the type of apparatus used.

Method of administration
Subcutaneous or intravenous use.
Heparin is administered by subcutaneous or intravenous injection or by intravenous infusion after dilution with a suitable vehicle solution.

Subcutaneous injection
After mild skin disinfection, inject the heparin dose strictly subcutaneously into a loosely grasped skin fold of the abdomen, or the extensor side of the thigh, vertically to the longitudinal axis of the body, using a fine needle.
Remove any drops of injection solution from the exterior of the needle prior to injection, because heparin introduced in the puncture channel may cause superficial haematoma or, in rare cases, a local allergic reaction.
To avoid lymph drainage impairment in patients having undergone lymph node resection in the abdominal or uro-genital region, subcutaneous injection should be performed on the upper arm in these patients.

Infusion
For infusion the product can be diluted with the solutions listed in section "Instructions for storage / use / handling"

Overdose
Symptoms
Bleeding, in most cases from the skin, mucous membranes, wounds, in the gastro-intestinal tract, the urinary tract and the genital tract (e. g. epistaxis, haematuria, melaena, haematomas, pinpoint bleeding). Drop of blood pressure, decrease of the haematocrit or other symptoms may indicate concealed bleeding.

Treatment
Mild bleeding:
can be stopped by simply reducing the dose.

Moderate, not life-threatening bleeding:
Heparin should be discontinued.

Severe life-threatening bleeding:
After exclusion of other causes such as deficiency of coagulation factors or consumption coagulopathy) administration of **protamine** to abolish the heparin effect.
Protamine should be given with great caution and for life-threatening haemorrhage only, because complete neutralisation of heparin will be associated with an increased risk of thrombosis. Further treatment should be under ICU conditions and include close monitoring of the patient.
Protamine is a protein rich of arginine, which is most commonly used in the form of its chloride or sulphate. As a rule, 1 mg of protamine will neutralise 100 I.U. of heparin. The serum half life time and the route of administration of heparin should be considered.

Thus,
- 90 min after intravenous administration of heparin, only half of the calculated amount of protamine should be given,
- 3 hours after heparin administration, only 25 % of the calculated protamine dose.

Overtitration with protamine may activate fibrinolysis and thus itself cause an increased tendency to bleeding. Too rapid i.v. injection of protamine may cause drop of blood pressure, bradycardia, dyspnoea, and sensation of discomfort. Protamine is eliminated from the circulation more rapidly than heparin. The efficacy of neutralisation is to be controlled by determinations of thrombin time and aPTT.
Heparin is not dialysable.

Undesirable effects
General
The most frequent but in most cases not serious undesirable effects are local reactions at the site of administration.
Besides this, bleeding complications may occur.
Heparin-induced thrombocytopenia of type II occurs rarely (< 1/1 000) but this adverse reaction may become serious. It is assumed to be a hypersensitivity reaction mediated by specific antibodies. Details see below.
Other undesirable effects may include local or systemic allergic reactions.

Undesirable effects are listed according to their frequencies as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)

Blood and lymphatic system disorders
Very common
Depending on the dose, increased incidence of bleeding, e.g. bleeding from the skin, mucous membranes, wounds, in the gastro-intestinal tract, the urinary tract and the genital tract. Bleeding complications may also affect organs, e.g. brain and lungs.

Common
At the beginning of heparin therapy mild heparin-induced thrombocytopenia not mediated by antibodies (platelet count 100 000 - 150 000 per microlitre), without thrombosis.

Immune system disorders
Uncommon
Systemic allergic reactions including nausea, headache, rise of temperature, limb pain, urticaria, vomiting, pruritus, dyspnoea, bronchospasm, and drop of blood pressure, local and general hypersensitivity reactions such as angiooedema

Rare
- Toxic or anaphylactoid reactions to benzyl alcohol
- Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia, details see below)

Very rare
- Anaphylactic shock especially in sensitized patients having previously received heparin.
- Onset of type II thrombocytopenia with a delay of up to several weeks after the end of heparin administration.

Endocrine disorders
Rare
Hypoaldosteronism, resulting in hyperkalaemia and metabolic acidosis, especially in patients with impaired kidney function and diabetes mellitus.

Vascular disorders
Very rare
Vasospasm.

Hepato-biliary disorders
Very common
Increases of the serum concentrations of transaminases (GOT, GPT), gamma-glutamyl transpeptidase, lactate dehydrogenase and lipase, which are, however, reversible and of no clinical significance.

Skin and subcutaneous tissue disorders
Uncommon: Transient alopecia, skin necroses.

Musculoskeleta and connective tissue disorders
After prolonged administration (over months), especially after high doses and in predisposed patients, osteoporosis may develop.

Reproductive system and breast disorders
Very rare
Priapism

General disorders and administration site conditions
Common
Local tissue reactions at the injection site, such as induration, redness, discoloration, and minor haematomas

Very rare
Calcinosis at the site of injection, mainly in patients with severe renal failure

Information on particular undesirable effects
Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia), is characterised by platelet counts markedly below 100 000 per microlitre or a rapid decrease to less than 50 per cent of the initial value and accompanied by arterial or venous thromboses or embolism, consumption coagulopathy, skin necroses at the site of injection, pinpoint bleeding (petechia), and tarry stools (melaena). The anticoagulatory effect of heparin may be reduced.
In patients without pre-existing hypersensitivity to heparin the decrease of the platelet count typically begins between 6 to 14 days after commencement of the heparin therapy. In patients with existing hypersensitivity to heparin such decrease may begin already after a few hours.
As soon as type II thrombocytopenia occurs, heparin administration must be discontinued immediately. Emergency treatment depends on the nature and severity of the symptoms. Re-exposure of the patient to parenteral heparin is absolutely contraindicated.

Note:
Patients should inform their doctor or pharmacist if they notice any side effect not mentioned in this leaflet.

Expiry date
Do not use the product beyond the expiry date stated on the labelling.

Instructions for storage / use / disposal / handling
Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not administer if solution shows signs of deterioration, i.e. turbidity, precipitate or discoloration, or if the container is damaged.
A vial can be stored for up to 14 days following first withdrawal, provided the solution withdrawn under strictly aseptic conditions. The date of first opening must be noted on the label.

For infusion the product can be diluted with the following solutions:
- Sodium Chloride 9 mg/ml solution for infusion
- Glucose 50 mg/ml or 100 mg/ml solution for infusion
- Sodium Chloride 4.5 mg/ml and Glucose 25 mg/ml solution for infusion
- Ringer's solution for infusion.

Dilutions with these solutions are chemically and physically stable at room temperature (25±2 °C) for 48 hours. From a microbiological point of view, dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

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B. Braun Melsungen AG
34209 Melsungen
Germany

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