Heparin Sodium B. Braun 5 000 IU/ml Solution for Injection/Infusion

1. NAME OF THE MEDICINAL PRODUCT

Heparin Sodium B. Braun 5 000 IU/ml Solution for Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection/infusion contains 5 000 IU of heparin sodium (porcine mucosa) according to WHO standard

1 vial (5 ml) contains 25 000 IU of heparin sodium

Excipients with known effect:
1 ml of solution for injection/infusion contains
12.5 mg benzyl alcohol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless or almost colourless aqueous solution.

pH 5.5–6.5

Osmolality: 270–330 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Therapy of acute venous and arterial thromboembolism (including early treatment of myocardial infarction and unstable angina pectoris);
- Prophylaxis of thromboembolism;
- Prevention of blood clotting during extracorporeal circulation (e.g. cardiopulmonary bypass, haemodialysis).

4.2 Posology and method of administration

Determine the heparin dose individually for each patient.

The dosage depends on the actual values of blood coagulation parameters (see also section **4.4**), 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 (see also section 4.4).

Recommended dosages

Therapy of acute venous and arterial thromboembolism (including early treatment of myocardial infarction and unstable angina pectoris)

Therapeutic dosing should be adjusted based on a regular monitoring of the aPTT, see section 4.4

Adults:

Bolus	Maintenance
80 IU/kg BW intravenously	18 IU/kg BW per hour intravenous infusion
5 000 IU intravenously*	Not less than 30 000 IU per day*
5 000 IU intravenously*	250 IU/kg BW twice daily subcutaneously
333 IU/kg BW subcutaneously	250 IU/kg BW twice daily subcutaneously

* Non-weight-based dosing recommendation intended for an average patient weighing 70 kg

Therapy of unstable angina pectoris or *non-ST elevation* myocardial infarction:

Bolus	Maintenance
60 – 70 IU/kg BW (maximum dose 5 000 IU) intravenously	12 – 15 IU/kg BW per hour (maximum 1 000 IU per hour) intravenous infusion

Therapy of ST elevation myocardial infarction in conjunction with fibrinolytic agents:

Bolus	Maintenance
60 IU/kg BW (maximum 4 000 IU) intravenously	12 IU/kg BW per hour (maximum 1 000 IU per hour) intravenous infusion

Paediatric population

Intravenous administration:
Neonates see section 4.3

Infants and toddlers 1 month – 1 year of age:

Bolus	Maintenance
75 IU/kg BW	25 IU/kg BW per hour, adjusted according to aPTT

Toddlers, children and adolescents 1 – 18 years of age:

Bolus	Maintenance
75 IU/kg BW	20 IU/kg BW per hour, adjusted according to aPTT

Subcutaneous administration:
Neonates see section 4.3
Infants, toddlers, children and adolescents 1 month – 18 years of age:
250 IU/kg BW twice daily, adjusted according to aPTT.

Prophylaxis of thromboembolism

Adults:

5 000 IU every 8 or 12 hours subcutaneously usually for at least 5 days or until discharge, if earlier.
In patients undergoing surgery the first dose is to be given 2 hours before surgery and thromboprophylaxis should be continued for 2 – 3 weeks after surgery.

Paediatric population:

Neonates see section 4.3
Infants, toddlers, children and adolescents 1 month – 18 years of age:
100 IU/kg BW (max. 5 000 IU) twice daily as subcutaneous injection, adjusted according to aPTT.

Prevention of blood clotting during extracorporeal circulation (e.g. cardiopulmonary bypass, haemodialysis)

Cardiopulmonary bypass:

300 – 400 IU/kg BW plus additional doses to achieve and maintain Activated Clotting Time > 480 seconds.

Haemodialysis:

50 IU/kg BW into arterial line, maintenance: 500 – 1500 IU per hour.

Special patient groups

Patients with hepatic or renal impairment
Dose reduction may be needed in patients with hepatic or renal impairment. See also section 4.4.

Elderly patients
Dose requirements for heparin might be adjusted in the elderly depending on their individual condition (e.g. kidney function). See also section 5.2.

Smokers
Depending on the amount of nicotine present in the body increased dosages might be necessary. Please refer also to section 4.5.

Obese patients
Clinical trials suggest that in order to provide sufficient anti-coagulation in morbidly obese patients increased maintenance dosages of heparin might be needed. However no specific dosage recommendations can be made.

Pregnancy
Therapy of thromboembolism:
Twice daily subcutaneous injections with or without initial intravenous bolus. The dosing should be adjusted according to aPTT taken 6 hours after each injection. See also sections 4.4, 4.6 and 4.8.
The treatment is to be continued for at least 6 weeks post-partum (for a minimum total duration of therapy of three months).

Patients with heparin resistance:
See section 4.4.

Method of administration

Subcutaneous or intravenous use.

The medicinal product is administered by subcutaneous or intravenous injection or by intravenous infusion after dilution with a suitable vehicle solution.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

The medicinal product must not be used in the following conditions:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Known hypersensitivity to pork products
- Active bleeding
- Heparin-induced thrombocytopenia of type II either known from the patient's history or being suspected on grounds of clinical observations
- Diseases and organ lesions associated with haemorrhagic diathesis, such as:
  - coagulopathies
  - thrombocytopenia
  - severe diseases of liver and pancreas
- Diseases where there is a suspicion of vascular damage, e.g.
  - ulcers in the gastro-intestinal tract
  - uncontrolled and severe arterial hypertension with a diastolic blood pressure higher than 110 mm Hg
  - intracranial haemorrhage
  - cerebral arterial aneurysm
  - retinopathies, bleeding into the vitreum
  - ophthalmic surgical procedures or injury
  - active tuberculosis
  - infectious endocarditis
- Imminent abortion

Because Heparin Sodium B. Braun contains benzyl alcohol, its use is contraindicated in neonates, especially in immature pre-term neonates.

4.4 Special warnings and precautions for use

Administration of the medicinal product should normally be avoided in the following conditions, unless their expected benefits clearly outweigh possible risks:

- Risk of bleeding (e.g. suspected malignant tumour, major surgery especially of the central nervous system, nephro- and ureterolithiasis);
- Chronic alcohol abuse.

Especially careful medical monitoring is required:

- if heparin is to be administered over prolonged periods during pregnancy (see also sections 4.6 and 4.8),
- in elderly patients, especially elderly women,
- critical ill patients,
- during medication with medicinal products affecting platelet function or the coagulation system (see section 4.5).

Care should be taken when the medicinal product is administered to patients with hypertension.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia. Therefore 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). See also section 4.5.

Neuraxial anaesthesia in patients treated with heparin is associated with higher risk of spinal bleeding and development of spinal haematoma that might cause long-term or even permanent paralysis. See also section 4.8.

A minimum time interval of 4 hours is required between the last dose of heparin and the insertion of the epidural/spinal needle or withdrawal of the catheter. If heparin is administered in therapeutic doses normalization of aPTT is required. Heparin administration may be restarted 1 hour after the procedure.

During therapy with heparin, i.m. injections should be avoided because of the risk of haematoma.

If thromboembolic complications occur during therapy with heparin, type II heparin-induced thrombocytopenia must be considered and platelet count should be performed.

Patients under heparin therapy should not be exposed to the risk of injuries.

After prolonged administration, osteoporosis may develop, especially in predisposed patients (i.e. older people - especially postmenopausal women, pregnant and breastfeeding women, and children). See also sections 4.6 and 4.8.

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.

Therapeutic dosing of heparin has to be monitored by use of a locally calibrated aPTT assay with a recommended therapeutic aPTT range of 1.5-2.5.

The aPTT should be monitored at least once daily with repeated measurement at around 4 h after each dose adjustment.

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 start of treatment and at days 5, 7 and 9. In patients with recent heparin exposure the platelet count should additionally be determined 12-24 hours after start of the treatment.

Heparin may affect the prothrombin time; this should be considered when determining the dosage of coumarin derivatives.

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

Special patient groups

Patients with hepatic or renal impairment

If heparin is administered to patients with hepatic or renal impairment, close monitoring including checks of the coagulation status is mandatory. This also applies to the use of heparin for prophylaxis of thromboembolism ("low-dose" therapy). In patients with hepatic or renal impairment there is a risk of benzyl alcohol accumulation leading to benzyl alcohol toxicity (metabolic acidosis).

Pregnancy

If available, heparin without preservatives is recommended when heparin therapy is needed during pregnancy. There are no known adverse outcomes associated with foetal exposure to the preservative benzyl alcohol by mothers after administration of the drug. However, as benzyl alcohol can cross the placental barrier, heparin with benzyl alcohol is preferably not administered during pregnancy.

Administration of therapeutic doses of heparin should be discontinued at least 24 hours before induction of labour or caesarean section.

Paediatric population

Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. See sections 4.6 and 4.8.
Since there is an increased risk of accumulation of benzyl alcohol in young children (less than 3 years old) this medicinal product should usually not be given for more than a week.
If heparin is administered to infants or children, close monitoring including checks of the coagulation status is mandatory. This also applies to the use of heparin for prophylaxis of thromboembolism ("low-dose" therapy).

Heparin resistance

Some patients require unusually high doses of heparin to achieve the therapeutic aPTT level (heparin resistance). In some cases this may be attributed to a varying responsiveness of the aPTT assay. Therefore administration of increased doses of heparin in patients with heparin resistance may only be executed based on additional anti-Xa level measurements (target range of 0.35 – 0.7 IU/ml).

Special warnings/precautions regarding excipients

This medicinal product contains 12.5 mg benzyl alcohol per ml.
See sections 4.3, 4.4 'Pregnancy' and 'Paediatric population', 4.6 and 4.8.
This medicinal product contains up to 25 mg sodium per vial, equivalent to 1.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction 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 high dose acetylsalicylic acid, ticlopidin, clopidogrel, dipyridamol, glycoprotein-IIb/IIIa receptor blockers
- fibrinolytics,
- other anticoagulants (e.g. coumarin derivatives, fondaparinux, dabigatran, other heparins or heparin-like substances),
- some non-steroidal anti-inflammatory drugs (e.g. ketorolac, intravenous diclofenac),
- high-dose penicillin,
- cytostatic drugs, except doxorubicin
- dextrans

Weakening of the heparin effect

The heparin effect may be weakened by:

- *doxorubicin*
- *nitrates:* reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.
- *basic drugs (e.g. phenothiazine, tricyclic psychopharmaca, antihistaminics):* weakening the effect of each other by building salts).

Influence of heparin on the effect of other drug substances:

Drugs that lead to an increase of the serum potassium level (e.g. aliskiren, ACE inhibitors) should only be administered together with heparin under careful monitoring. See also section 4.4.
Heparin is known to activate plasma lipoprotein lipase, which should be taken into consideration when heparin is administered concomitantly together with drugs with known high plasma protein binding and narrow therapeutic width (e.g. cardiac glycosides).

Nicotine abuse:

Nicotine may increase the clearance of heparin and therefore partially counteracts the anticoagulant effect of heparin. See also section 4.2.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicate no malformative or foetal/ neonatal toxicity of heparin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Heparin does not cross the placental barrier.

During pregnancy, complications resulting from underlying illness and/or treatment cannot be excluded.

In addition, this medicinal product contains benzyl alcohol, which may cross the placental barrier. Because of the potential harm of benzyl alcohol to the foetus (see section 4.3 and 4.4), the benefit of heparin for the mother should be weighed against the potential risk for the foetus.

Long-term administration of heparin may increase the risk of osteoporosis in pregnant women (see also section 4.4).

The tendency for skin lesions is higher in pregnant women compared to non-pregnant women (see section 4.4 and 4.8).

For the use of heparin in epidural anaesthesia during labour see section 4.4.

For imminent abortion (see also section 4.3).

Breast-feeding

Heparin/metabolites are not excreted in human milk. However, the preservative benzyl alcohol contained in Heparin B. Braun is likely to be excreted in human milk and may be absorbed by a nursing infant. Therefore caution has to be applied when administering Heparin B. Braun to a nursing mother. If available preservative-free Heparin Sodium Injection/Infusion should be preferred. Long-term administration of heparin may increase the risk of osteoporosis in breast-feeding women (see also section 4.4).

Fertility

In patients with APLA syndrome ante-partum prophylaxis with heparin is recommended.
No information is available on adverse effects of heparin on fertility. In contrast, according to available literature heparin generally is considered to be more beneficial rather than being of disadvantage.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent undesirable effects are bleeding events from any organ or tissue.

Besides this, local reactions at the site of administration may occur.

Heparin-induced thrombocytopenia of type II occurs rarely (≥ 1/10 000 to < 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.

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Directions for Use

Heparin Sodium B. Braun 5 000 IU/ml Solution for Injection/ Infusion

B. Braun Melsungen AG
34209 Melsungen
Germany

Listing of undesirable effects

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)
Not known	Frequency cannot be estimated from the available data

All reactions that are derived from post-marketing experience (spontaneous reports and literature) only are based on a patient population which is largely unknown. Therefore exact incidences cannot be provided and are referred to with the frequency 'not known'.

Blood and lymphatic system disorders

Common:

Heparin-induced thrombocytopenia type I

At the beginning of heparin therapy mild heparin-induced thrombocytopenia type I (platelet count 100 000 – 150 000 per microlitre), without thrombosis. The thrombocytopenia usually occurs within the first 5 days of treatment, and is probably due to a direct effect on platelets.

Not known:

Eosinophilia.

Nervous system disorders

Not known:

Permanent or temporary paralysis due to subarachnoidal or epidural haematomas after neuraxial anaesthesia.
Toxic reactions due to benzyl alcohol.

Skin and subcutaneous tissue disorders

Uncommon:

Transient alopecia following long-term administration, skin necroses

Musculoskeletal and connective tissue disorders

Not known:

Osteoporosis (after long-term administration of heparin) (see also sections 4.4 and 4.6).

Endocrine disorders

Rare:

Hypoaldosteronism, resulting in hyperkalaemia and metabolic acidosis, especially in patients with impaired kidney function and diabetes mellitus. See also section 4.4.

Vascular disorders

Very common:

Haemorrhage; see also sections 4.4 and 4.9.
Depending on the dose, increased incidence of bleeding from any organ or tissue.

General disorders and administration site conditions

Common:

Local tissue reactions at the injection site, such as induration, redness, discolouration, and minor haematomas

Immune system disorders

Uncommon:

Allergic reactions of all types and severities, with various manifestations (e.g. urticaria, pruritus, dyspnoea, bronchospasm, hypotension).

Rare:

- Allergic reactions to benzyl alcohol
- Severe heparin-induced, antibody-mediated thrombocytopenia (Heparin-induced thrombocytopenia type II, 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.

Not known:

- Type IV hypersensitivity reaction (e. g. skin lesions, erythematous papules and plaques located at injection site) which may occur with a latency of up to several months

Hepatobiliary disorders

Very common:

Hepatic enzymes increased (increases of the serum concentrations of transaminases (AST, ALT), gamma-glutamyl transpeptidase, lactate dehydrogenase and lipase, possible resulting in increased free fatty acids). These reactions are, however, reversible.

Reproductive system and breast disorders

Very rare:

Priapism.

Information on particular undesirable effects

Heparin induced thrombocytopenia type II

Severe heparin-induced, antibody-mediated thrombocytopenia (type II thrombocytopenia, HIT II), 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. 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 5 to 14 days after commencement of the heparin therapy. In patients with existing antibodies to heparin such decrease may begin already after a few hours. The greater the degree of trauma and thus the release of PF4, the more likely patients went on to develop HIT antibodies and clinical HIT.

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.

Patients undergoing extracorporeal circulation.

Principally the same ADRs that occur in other patients might occur. Haemodialysis patients might be at an increased risk for developing anaphylactic or anaphylactoid reactions.

4.9 Overdose

Symptoms

Bleeding, in most cases 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. Drop of blood pressure, decrease of the haematocrit, or other symptoms may indicate concealed bleeding.

Treatment

Mild or 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.
The serum half-life and the route of administration of heparin should be considered.
Protamine is eliminated from the circulation more rapidly than heparin. The efficacy of neutralisation is to be controlled by determinations of aPTT.

Heparin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

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

Mechanism of action, therapeutic effect

Heparin is an acidic and polydisperse polysaccharide. Due to its negative charge it forms complexes with certain proteins, changing their biological activities. In particular, antithrombin III (AT) is activated by a factor of about 1 000 by complex formation with heparin. Only approximately one-third of an administered heparin dose bind to antithrombin III (AT) resulting in a complex, and this fraction is responsible for its anticoagulant effect. The remaining two-thirds have minimal anticoagulant activity (about 15 %) at therapeutic concentrations, but when concentrations are higher than those in the therapeutic range, both high-affinity and low-affinity heparin catalyze the antithrombotic effect of heparin cofactor II (HC II).

Activated antithrombin inhibits various serine proteases, among these the coagulation factors XIIa, XIa, Xa, IXa, VIIa, and IIa. Factor VIIa is only moderately sensitive, IIa (thrombin) and Xa, in contrast, are highly sensitive to the action of the AT-heparin complex. Low heparin doses predominantly accelerate the inactivation of factor Xa. This explains the efficacy of low dose heparin in the prophylaxis of thromboembolism. The anticoagulatory effect of heparin depends on the concentrations of antithrombin and of fibrinogen. Higher heparin doses inactivate thrombin formed in excess and thus prevent the formation of fibrin from fibrinogen. Heparin also affects the platelet function.

Certain substances contained in platelets (platelet factor 4) neutralise heparin.

Heparin is known to activate plasma lipoprotein lipase (see section 4.5).
Effect on bone formation: Independently of its anticoagulant activity heparin has been shown to suppress osteoblast formation and activates osteoclasts.

Paediatric population

Plasma concentrations of antithrombin are physiologically low at birth (approximately 0.5 IU/ml) and do not increase to adult values until 3 months of age. Besides the need for increased doses in children, physiologically decreased antithrombin during the first months of life may limit the UFH effectiveness, as well as disease states that further decrease plasma concentrations of AT (i.e. nephrotic syndrome, liver cirrhosis, L-asparaginase treatment for acute lymphoblastic leukaemia), and increased plasma concentrations of acute phase proteins that bind heparin.

The capacity of plasma from neonates to generate thrombin is both delayed and decreased compared to that in adults, and is similar to plasma from adults receiving therapeutic amounts of heparin. Following infancy, the capacity of plasma to generate thrombin increases but remains approximately 25 % less than for adults throughout childhood (See also section 4.2).

5.2 Pharmacokinetic properties

Absorption

Because of its high relative molecular mass and its negative surface charge heparin is not absorbed from the intestine, but intake by parenteral route (i.v. or s.c.) or inhalation is possible.

Bioavailability

When given by intravenous injection the effect of heparin sets on immediately after administration.

Once administered s.c. heparin follows non-linear kinetics, as there is a combination of saturable and non-saturable mechanisms of clearance. This effect thereby reduces the unbound fraction of heparin and also heparin's anticoagulant activity at low concentrations. Additionally, binding of heparin to Von-Willebrand-factor inhibits platelet function. The bioavailability of subcutaneously administered heparin is dose-dependent. The bioavailability of the anti-factor Xa activity increases with the dose delivered and tends from approximately 30 % with low doses toward 100 % at high doses. Therefore after subcutaneous injection, the onset of the heparin effect is delayed for approximately 0.5-1 hour after administration.

If an immediate anticoagulant effect is required, the initial dose administered s.c. should be accompanied by an i.v. bolus injection.

Distribution

Heparin is strongly bound to plasma proteins (LDL, globulins, in particular AT and fibrinogen). Therefore the distribution volume is generally limited to the plasma volume. This is also valid for adults undergoing dialysis; here the volume of distribution has been reported to be approx. 0.07 l/kg.

Biotransformation and elimination

After parenteral administration heparin is eliminated from the blood through a combination of rapid saturable mechanism of zero-order and much slower first-order mechanism. The saturable phase of heparin clearance is attributed to binding to the reticulo-endothelial system (e.g. endothelial cell receptors, macrophages), where it is internalized and depolymerised followed by its degradation in the liver by heparinases and urinary excretion mainly in the form of depolymerized inactivated heparin. The interindividual half-life has been reported to be approximately 1 – 2 hours. It depends on the actual dose administered, on liver and kidney function and on accompanying diseases.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional data of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, toxicity to reproduction and development.

In animal studies only effects have been observed that have already been described also for humans in section 4.8, such as osteoporosis and bleeding.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (antimicrobial preservative), 12.5 mg/ml

Hydrochloric acid (for pH adjustment)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Heparin forms salts with alkaline drug substances (tricyclic psychotropic agents, antihistamines, or quinine) leading to mutual weakening of their effects.

Heparin is incompatible with many injectable preparations e.g. some antibiotics, opioid analgesics and antihistamines.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened

3 years

After first opening the container

A vial can be stored for up to 14 days following first withdrawal, provided the solution is withdrawn under strictly aseptic conditions. The date of first opening must be noted on the label.

After dilution according to directions

Dilutions with the solutions stated in section 6.6 are chemically and physically stable at room temperature 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.

6.4 Special precautions for storage

Do not store above 30°C.

Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vials (type II Ph. Eur.) sealed with a rubber stopper.
Content:
5 ml

Pack sizes:
10 x 5 ml

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Do not administer if solution shows signs of deterioration, i.e. turbidity, precipitate or discoloration, or if the container is damaged.

For intravenous infusion, Heparin Sodium may be diluted with the following solutions for infusion:

- Sodium chloride 9 mg/ml solution for infusion
- Glucose 50 mg/ml or 100 mg/ml solution for infusion
- Ringer's solution for infusion.

Dilutions with these solutions are stable at room temperature for 48 hours.

7 DATE OF REVISION OF THE TEXT

01.2020