SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SELOPARIN 25 000 IU/5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule (5 ml) contains;

Active ingredient:

25 000 IU heparin sodium

Excipients:

Benzyl alcohol	47.25 mg
Sodium chloride	45 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for 5 ml ampoule

Almost colourless, clear solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SELOPARIN is indicated mainly at diseases below:

- Prophylaxis of deep vein thrombosis, pulmonary embolism and arterial thromboembolic events.
- Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion.
- Prophylaxis of mural thrombosis following myocardial infarction.
- In extracorporeal circulation and haemodialysis.

4.2. Posology and method of administration

Posology:

Use intravenously or subcutaneously. It should not be administered intramuscularly.

The concentration of heparin solution is 5000 IU / ml. Heparin dose as IU must be specified for all heparin preparations does not contain same concentration.

Application frequency and time:

- Prophylaxis of deep vein thrombosis, pulmonary embolism and arterial thromboembolic events:

2 hours preoperatively:	5,000 units subcutaneously
followed by:	5,000 units subcutaneously every 8-12 hours, for 7-10 days or until the patient is fully ambulant.

No laboratory monitoring should be necessary during low dose heparin prophylaxis. If monitoring is considered desirable, anti-Xa assays should be used as the activated partial thromboplastin time (APTT) is not significantly prolonged.

Laboratory tests should be performed daily. Ideally, every day the same hours and 6 hours after the start of the first sample treatment, then after each dose in exchange for 4-6 hours should be taken. During the whole dose of heparin therapy, daily laboratory monitoring, activated part thromboplastin time (aPTT) adjusting or controlling 1.5-2 times the value of the midpoint of the normal range is essential.

- Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion:

Loading dose:	5,000 units intravenously (10,000 units may be required in severe pulmonary embolism)
Maintenance:	1,000-2,000 units/hour by intravenous infusion, or 10,000-20,000 units 12 hourly subcutaneously, or 5,000-10,000 units 4hourly by intravenous injection.

- Prophylaxis of mural thrombosis following myocardial infarction:

12,500 units 12 hourly subcutaneously for at least 10 days.

- In extracorporeal circulation and haemodialysis:

Cardiopulmonary bypass: Initially 300 units/kg intravenously, adjusted thereafter to maintain the activated clotting time (ACT) in the range 400-500 seconds.

Haemodialysis and haemofiltration:

Initially 1,000-5,000 units,

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

Route of administration:

By continuous intravenous infusion in 5% glucose or 0.9% sodium chloride or by intermittent intravenous injection, or by subcutaneous injection.

Heparin intravenous injection volume should not exceed 15 ml.

As the effects of heparin are short lived, administration by intravenous infusion or subcutaneous injection is preferable to intermittent intravenous injections.

Additional information on special populations:

Renal / Hepatic impairment

It should be administered with caution. In patients with advanced renal or hepatic disease, a reduction in dosage may be necessary. The risk of bleeding is increased with severe renal impairment and in the elderly (particularly elderly women).

Pediatric population

- Prophylaxis of deep vein thrombosis, pulmonary embolism and arterial thromboembolic events:

No dosage recommendations.

- Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion:

Loading dose: 50 units/kg intravenously

Maintenance: 15-25 units/kg/hour by intravenous infusion,
or 250 units/kg 12 hourly subcutaneously
or 100 units/kg 4hourly by intravenous injection.

Pregnant

5,000-10,000 units every 12 hours, subcutaneously, adjusted according to aPTT or anti-Xa assay.

4.3. Contraindications

SELOPARIN should not be used in the following cases:

- Hipersensivity to heparin or excipients of drug content.
- Premature babies or newborns (because it contains benzyl alcohol)

- Patients who consume large amounts of alcohol, who are sensitive to the drug, who are actively bleeding or who have haemophilia or other bleeding disorders, severe liver disease (including oesophageal varices), purpura, severe hypertension, active tuberculosis or increased capillary permeability.
- Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contraindicates the further use of heparin either by subcutaneous or intravenous routes because of the risk of thrombocytopenia. Because of the special hazard of postoperative haemorrhage heparin is contraindicated during surgery of the brain, spinal cord and eye, in procedures at sites where there is a risk of bleeding, in patients that have had recent surgery, and in patients undergoing lumbar puncture or regional anaesthetic block.

The relative risks and benefits of heparin should be carefully assessed in patients with a bleeding tendency or those patients with an actual or potential bleeding site eg. hiatus hernia, peptic ulcer, neoplasm, bacterial endocarditis, retinopathy, bleeding haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or threatened abortion.

4.4. Special warnings and precautions for use

Heparin-treated (curative or prophylactic doses) in a patient;

- if ischemic stroke,
- if myocardial infarction,
- if acute ischemia in the lower limbs,
- if pulmonary embolism,
- if phlebitis,
- if thrombotic events such as thrombosis aggravation,

Heparin-induced thrombocytopenia (HIT) should be systematically considered and platelets (platelet) count test should be carried out urgently.

Precautions

At risk situations:

Lumbar puncture performance should be considered for intraspinal bleeding risk in postoperative period after the brain and spinal cord surgery or in patients with peptic ulcer, choroidal and retinal vascular disease a history. It should be delayed as much as possible.

Monitoring of platelet counts:

Regardless of the administered dose and indication, platelets depending on the risk of HIT should be monitored. Once before the treatment, then 2 times a week for 21 days, platelet counts should be performed. After this period, in which case the exact extension of the treatment, the frequency of monitoring of the platelet count should be increased to 1 per week until treatment is stopped.

Heparin can suppress adrenal secretion of aldosterone. In this case leads to hyperkalemia and/or metabolic acidosis with hypoaldosteronism. This event was observed in high risk patients with high blood levels of potassium (diabetic patients, patients with chronic renal failure, patients with metabolic acidosis story, patients using medications that increase the blood level of potassium such as ACE inhibitors and NSAID). The risk of hyperkalemia increases during treatment and is usually reversible. Plasma potassium levels should be monitored in case of prolonged treatment in high risk patients. Plasma potassium levels should be measured before the heparin treatment for patients at risk and all patients treated for more than 7 days.

Heparin-induced thrombocytopenia (HIT):

There is the risk of immunological origin heparin-induced thrombocytopenia, known as type II thrombocytopenia, causing thrombosis (unfractionated heparin and less frequently caused by low molecular weight heparins) sometimes.

HIT is determined by two consecutive measurements with a significant decrease in platelet count by 30-50% and/or <100 000 worth of platelet count. It develops between 5-21th days following administration of heparin (with a peak incidence of 10 days), but during the treatment with heparin in patients with a history of thrombocytopenia may occur earlier. As a result, a story of this type should be investigated systematically during in-depth interviews. In addition, the risk of relapse to drug rechallenge case can take several years or even a lifetime (see also Contraindications).

Platelet measurement must be done in 5 days more than heparin-treated patients. Treatment should be discontinued immediately in patients with thrombocytopenia development.

In all cases, the beginning of HIT is an emergency and requires specialist advice.

Any significant decrease in platelet count (initial value of 30-50%, i) should be seen as a signal before the value reaches critical levels. The observed decrease in the number of platelets;

- Emergency a platelet count
- If the decrease is confirmed, require cessation of heparin therapy.

Under these circumstances, things to emergency measures does not depend on the results of in vitro or immunological platelet aggregation tests. Because only some specialized laboratories routinely conducts these tests and the results obtained after a few years the best possibility. These tests must still be performed to aid in the diagnosis of complications. If you continue to treat, thrombosis is a major risk.

- Treatment and prevention of thrombotic complications of HIT

If deemed necessary to continue anticoagulation, heparin must be replaced with another class of antithrombotic agents. Danaparoid sodium or hirudin, depending on the situation is given in prophylactic or curative doses.

Replaced by oral anticoagulant drugs depending on the risk of thrombotic cases exacerbated with oral anticoagulants should occur only once, when platelet count returned to normal.

Although even though rare heparin to hipersensivity, a trial dose of 1000 IU is recommended to be administered patients with a history of allergy. Care must be exercised in patients with hypersensitivity to low molecular weight heparins.

Recommended low dose regimen, the majority of patients, does not create a change in coagulation time. However, the effect on blood coagulation therapy should be kept under observation in major surgery of patients with a individual response to heparin.

Care should be taken in case of spinal or epidural anesthesia (risk of spinal hematoma).

Heparin resistance

There is considerable variation in individual anticoagulant responses to heparin.
Heparin resistance, defined as an inadequate response to heparin at a standard dose for achieving a therapeutic goal occurs in approximately 5 to 30% of patients.

Factors predisposing to the development of heparin resistance, include:

• Antithrombin III activity less than 60% of normal (antithrombin III dependent heparin resistance):

Reduced antithrombin III activity may be hereditary or more commonly, acquired (secondary to preoperative heparin therapy in the main, chronic liver disease, nephrotic syndrome, cardiopulmonary bypass, low grade disseminated intravascular coagulation or drug induced, e.g. by aprotinin, oestrogen or possibly nitroglycerin)

• Patients with normal or supranormal antithrombin III levels (antithrombin III in dependent heparin resistance)
• Thromboembolic disorders
• Increased heparin clearance
• Elevated levels of heparin binding proteins, factor VIII, von Willebrand factor, fibrinogen, platelet factor 4 or histidinerich glycoprotein
• Active infection (sepsis or endocarditis)
• Preoperative intraaortic balloon counterpulsation
• Thrombocytopenia
• Thrombocytosis
• Advanced age
• Plasma albumin concentration ≤ 35g/dl

Heparin resistance is also often encountered in acutely ill patients, in patients with malignancy and during pregnancy or the postpartum period.
SELOPARIN contains 47.25 mg benzly alcohol as preservative. Caution needed when prescribing to suspected patients, especially infants. Benzly alcohol causes toxic and anaphylactoid reactions in babies and <3 years old children.
This medicinal product contains 33.21 mg sodium per 5 ml ampoule, equivalent to 0.066 % 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

Analgesics: Drugs that interfere with platelet aggregation eg. acetylsalicylic acid (analgesic and antipyretic doses), acetylsalicylic acid (at a dose which inhibits platelets) and other NSAIDs should be used with care. Increased risk of haemorrhage with ketorolac (avoid concomitant use even with lowdose heparin).

Corticosteroids (gluco-): excluding hydrocortisone used for replacement therapy in Addison's disease.

Anticoagulants, platelet inhibitors, etc: Increased risk of bleeding with oral anticoagulants, epoprostenol, clopidogrel, ticlopidine, streptokinase, dipyridamole, dextran solutions, or any other drug which may interfere with coagulation.

Cephalosporins: Some cephalosporins, e.g. cefaclor, cefixime and ceftriaxone, can affect the coagulation process and may therefore increase the risk of haemorrhage when used concurrently with heparin.

ACE inhibitors: Hyperkalaemia may occur with concomitant use.

Nitrates: Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.

Thrombolytic drugs: It may increase the risk of hemorrhagic. Patients should be monitored regularly.

Probenecid: May increase the anticoagulant effects of heparin.

Tobacco smoke: Nicotine may partially counteract the anticoagulant effect of heparin. Increased heparin dosage may be required in smokers.

Interference with diagnostic tests may be associated with pseudohypocalcaemia (in haemodialysis patients), artefactual increases in total thyroxine and triiodothyronine, simulated metabolic acidosis and inhibition of the chromogenic lysate assay for endotoxin. Heparin may interfere with the determination of aminoglycosides by immunoassays.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)

There is no study concerning the effect of heparin on women with childbearing potential/contraception.

Pregnancy

Heparin is not contraindicated in pregnancy. Heparin does not cross the placenta. The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstances.

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

Haemorrhage may be a problem during pregnancy or after delivery. Especially in utero placental hemorrhage due to measures taken at birth is required.

Lactation

Heparin does not appear in breast milk. Therefore, it is possible to breastfeed during treatment with heparin.

Reproductive ability/fertility

There is not enough study.

4.7. Effects on ability to drive and use machines

None stated.

4.8. Undesirable effects

Undesirable events are listed by system organ class and frequency with the following approach:

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); unknown (cannot be estimated from the available data)

The most frequently reported adverse events; hemorrhage, reversible increases in liver enzymes, reversible thrombocytopenia and various skin reactions. Isolated reports have been reported widespread allergic reactions, skin necrosis and priapism.

Blood and lymphatic system disorders

Rare: Thrombocytopenia has been observed occasionally.

Two types of heparininduced thrombocytopenia have been defined:

Type I is frequent, mild (usually >50 x 10^9/L) and transient, occurring within 1-5 days of heparin administration.

Type II is less frequent but often associated with severe thrombocytopenia (usually <50 x 10^9/L). It is immunemediated and occurs after a week or more (earlier in patients previously exposed to heparin). It is associated with the production of a plateletaggregating antibody and thromboembolic complications which may precede the onset of thrombocytopenia. Heparin should be discontinued immediately.

In some cases, thrombocytopenia type II is accompanied by venous or arterial thrombosis.

Immune system disorders

Rare: Any type and severe allergic reactions with various hypersensitivity symptoms (urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills)

Anaphylactic reaction and anaphylactic shock

Angioneurotic oedema

Metabolism and nutrition disorders

Rare: Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see Warnings and Precautions).

Vascular disorders

Rare: Haemorrhage. More may occur with high doses of heparin. (see also Special Warnings and Precautions and Overdosage Information).

Very rare cases of epidural or spinal hematoma, prophylaxis of spinal or epidural anesthesia or spinal puncture implementation in patients receiving heparin has been reported.

Hepatobiliary disorders

Rare: Elevated transaminases, gamma-GT, LDH and lipase levels They usually resolve after discontinuation of heparin.

Skin and subcutaneous tissue disorders

Common: Rash (erythematosus and various types rash such as maculopapular), urticaria, pruritus

Rare: Skin necrosis. Treatment should be stopped immediately if skin necrosis occurs.

Musculoskeletal and connective tissue disorders

Uncommon: There is some evidence that prolonged dosing with heparin (ie. over many months) may cause alopecia and osteoporosis. Significant bone demineralisation has been reported in women taking more than 10,000 I.U. per day of heparin for at least 6 months.

Reproductive system and breast disorders

Very rare: Priapism has been reported.

General disorders and administration site conditions

Very common: Injection site reactions; When injected into the skin under local irritation may occur.

Reportig of the side side

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

A potential hazard of heparin therapy is haemorrhage, but this is usually due to overdosage and the risk is minimised by strict laboratory control. Slight haemorrhage can usually be treated by withdrawing the drug. If bleeding is more severe, clotting time and platelet count should be determined. Prolonged clotting time will indicate the presence of an excessive anticoagulant effect requiring neutralisation by intravenous protamine sulphate, at a dosage of 1 mg for every 100 I.U. of heparin to be neutralised. The bolus dose of protamine sulphate should be given slowly over about 10 minutes and not exceed 50 mg. If more than 15 minutes have elapsed since the injection of heparin, lower doses of protamine will be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents / heparin group

ATC code: B01AB01

Heparin is an anticoagulant agents at various stages of the effect of the normal coagulation system. It inhibits in vivo an in vitro reactions leading to blood clotting and the formation of fibrin clots. Antithrombin III (heparin co-factor) in plasma with heparin in small therapeutic dose combination inactivates activated factor X and inhibits trombosis by preventing the conversion of prothrombin to thrombin. This dose-dependently increased rate of inhibition. A greater amount of heparin, by in activating thrombin and preventing the conversion of fibrinojen to fibrin, may prevent further clot formation in the event of the occurrence of active thrombosis. Heparin also prevents the formation of a fibrin clot resistant by inhibiting the activation fibrin-stabilizing factor.

The heparin does not have fibrinolytic activity and therefore can not resolve the existing clot. Bleeding time is usually unaffected by heparin. Clotting time is prolonged full therapeutic doses of heparin, unaffected at low doses.

5.2. Pharmacokinetic properties

General features

Immediately after intravenous injection, and 20-30 minutes after subcutaneous injection shows the anticoagulant effect.

Absorption:

Heparin does not indicate the normal absorption in oral, rectal, intramuscular and subcutaneous administration. Subcutaneous administration form acceptable prophylactic use only.

Distribution:

Heparin does not cross the placenta and breast milk.

Metabolism:

Heparin is metabolized in the liver. A fraction of heparin is neutralized with various factors such as platelet factor IV, plasma proteins (including fibrinogen), the reticuloendothelial system. Metabolites are inactive.

Elimination:

Plasma half-life of heparin varies widely between individuals depending on the dose and type of use and is considered as an average of 90 minutes.

Heparin is eliminated by the kidneys and is excreted unchanged a small amount with urine.
Characteristic features of the patients

Elimination half-life time may vary depending on the presence of obesity, renal failure, malignancy, pulmonary embolism, liver dysfunction and infections.

The same amount of patients over 60 years of age dose compared to patients under 60 years old may have higher plasma levels of heparin and longer activated partial thromboplastin time.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol

Sodium chloride

Sodium hydroxide or hydrochloric acid

Water for injections

6.2. Incompatibilities

Any feasibility study was not carried out due to this product should not be mixed with other medicinal products.

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

The following drugs are incompatible with heparin;

Alteplase, amikacin sulphate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, chlorpromazine hydrochloride, ciprofloxacin lactate, cisatracurium besilate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, labetolol hydrochloride, meticillin sodium, methotrimeprazine, netilmicin sulphate, nicardipine hydrochloride, oxytetracycline hydrochloride, pethidine hydrochloride, polymyxin B sulphate, promethazine hydrochloride, streptomycin sulphate, tobramycin sulphate, trifluprомazine hydrochloride, vancomycin hydrochloride and vinblastine sulphate.

Dobutamine hydrochloride and heparin should not be mixed or infused through the same intravenous line, as this causes precipitation.

Heparin and reteplase are incompatible when combined in solution. If reteplase and heparin are to be given through the same line this, together with any Y-lines, must be thoroughly flushed with a 0.9% saline or a 5% glucose solution prior to and following the reteplase injection.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Please note that the application of the clear solution and the packaging is opened before.

Store at 25°C below room temperature and in the original packaging. Do not freeze.

The vial after once opening is available for a maximum of 28 days at 25°C.

Multidose vial is for single patient use.

6.5. Nature and contents of container

Bromobutyl stopper, red flip-off aluminum cap, type I colorless glass vial.

It is presented in boxes containing 1 vial.

6.6. Special precautions for disposal and other handling

Unused products or waste materials should be disposed of in accordance with the ' Medical Waste Control Regulations' and 'Packaging and Packaging Waste Control Regulations'

7. MARKETING AUTHORISATION HOLDER

Haver Farma İlaç A.Ş.

Akbaba Mah. Maraş Cad.
No:52/2/1 Beykoz/İSTANBUL/TURKEY
Tel: (0216) 324 38 38

Fax: (0216) 317 04 98

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253/39

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