SUMMARY OF PRODUCT CHARACTERISTICS

Heparin Sodium ROVI® 5,000 IU/ml,
Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Heparin Sodium ROVI 5,000 IU/ml
Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the product contains 5,000 IU of heparin sodium.
Each vial of 5 ml solution for injection contains 25,000 IU of heparin sodium (from porcine intestinal mucosa).

Excipient with known effect:
This medicine contains 10 mg benzyl alcohol in each ml, which is equivalent to 50 mg per vial of 5ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless or slightly yellowish, clear solution, free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Prevention of thromboembolic disorders.
- As part of the treatment of venous or arterial thromboembolic disorders (including the early treatment of heart attacks as well as unstable angina pectoris).
- For anticoagulation during treatment or operation with an extracorporeal circulation (e.g. heart/lung machine, haemodialysis).

4.2 Posology and method of administration

Dosage
Heparin sodium must be individually dosed.
The dosage depends on the coagulation parameters (see section 4.4) the nature and course of the disease, the patient's response, adverse reactions, and the patient's weight and age.
Differences in sensitivity to heparin and a possible change in heparin tolerance during the course of treatment need to be considered.

Prophylaxis of thromboembolism (low-dose treatment)
Subcutaneous injection is recommended for the prophylaxis of thromboembolism. Pre-filled syringes with an appropriate dosage are available for this.

General dosage recommendation for the prophylaxis of thromboembolism:
- *Pre- and postoperative prophylaxis of thromboembolism*
Preoperatively 5,000-7,500 IU subcutaneously approximately 2 hours before the operation. Postoperatively, depending on the risk of thrombosis, usually 5,000 IU subcutaneously every 8-12 hours or 7,500 IU subcutaneously every 12 hours until the patient is mobilised or until vitamin K antagonists have an adequate effect. Laboratory monitoring (coagulation parameters) for dose adjustment may be required in individual cases.

- *Prophylaxis in non-surgical medicine*
(e.g. prolonged bed rest, increased thrombotic tendency in the patient, diseases with an increased risk of thrombosis.)
Depending on the risk of thrombosis, generally 5,000 IU subcutaneously every 8-12 hours or 7,500 IU subcutaneously every 12 hours.
The dosage must be adapted to the risk of thrombosis and the level of activity of the coagulation system and can be determined by monitoring coagulation parameters.

As part of the treatment of venous or arterial thromboembolic disorders
Continuous intravenous administration is recommended if there are clots in blood vessels.

Dosage in adults
Generally start with 5,000 IU heparin sodium as an intravenous bolus, followed by a continuous infusion of 1,000 IU heparin sodium per hour using an infusion pump.

Dosage in children
Initially 50 IU/kg body weight, then 20 IU/kg body weight per hour.

If a continuous intravenous infusion is not possible, subcutaneous therapy (in 2-3 separate doses) may be used as an alternative, with close monitoring of therapy (e.g. 10,000-12,500 IU of heparin sodium every 12 hours).

Close monitoring of therapy accompanied by assay of coagulation parameters is absolutely essential in all cases. Monitoring of therapy and dose adjustment are generally based on activated partial thromboplastin time (aPTT), which should be around 1.5-2.5 times the normal value. It is recommended that the aPTT be checked 1-2 hours, 6 hours, 12 hours and 24 hours after the start of treatment in the case of continuous intravenous heparin administration, and 6 hours after administration of the second dose in the case of subcutaneous administration.

- *Treatment of venous thromboembolism*
Initially, 5,000 IU heparin sodium should be administered intravenously as a bolus, followed by an intravenous infusion of generally 1,000 IU heparin sodium per hour. The dosage should be adjusted according to the aPTT values, aiming to prolong the aPTT to 1.5-2.5 times the initial value (within the first 24 hours if possible).
The treatment should take place for at least 4 days or continued until adequate oral anticoagulation has been achieved.

- *As part of the treatment of unstable angina and non–Q-wave myocardial infarction*
In general, 5,000 IU heparin sodium as an intravenous bolus, followed by a continuous infusion of 1,000 IU per hour. The dose is based on the aPTT, which should be prolonged to 1.5-2.5 times the normal value.
Heparin sodium should be administered for at least 48 hours.

- *As concomitant therapy in thrombolysis with fibrin-specific thrombolytics (e.g. r-tPA) for the treatment of acute myocardial infarction*
Initially, 5,000 IU heparin sodium as an intravenous bolus, followed by an intravenous infusion of 1,000 IU per hour.
The infusion should be adjusted according to aPTT values to prolong them to about 1.5-2.5

times the initial value. Heparin sodium should be given for 48 hours.

In the case of thrombolysis with non-fibrin-specific thrombolytics (e.g. streptokinase), a subcutaneous injection of 12,500 IU heparin sodium may also be administered every 12 hours, starting 4 hours after thrombolysis.

The exact dosage of the concomitant heparin therapy depends on the type of thrombolytic and should be undertaken according to the data on the individual thrombolytic agents.
It is important to ensure accurate monitoring of the coagulation status in all cases.

Anticoagulation in treatment or surgery with an extracorporeal circulation
Haemodialysis
Individual dosage depending on the results of the coagulation tests and type of machine.

Heart/lung machine
The dosage depends on the type of heart/lung machine and the length of the operation and should be managed individually.

Method of administration
Subcutaneous and intravenous injection or intravenous infusion.

Administration of the subcutaneous injection
The injection should be administered with a fine injection needle held perpendicular to the body axis, into a raised fold of abdominal skin or on the anterior aspect of the thigh; the injection must be strictly subcutaneous. Any drops adhering to the injection needle should be removed before the injection, as introducing heparin sodium into the injection channel can result in superficial bruising and in rare cases local allergic irritation.

Notes:
To minimise disruption of lymph drainage, *Heparin Sodium Rovi 5,000 IU/ml* should be administered into the upper arm in patients with surgical clearance of lymph nodes in the abdominal/urogenital regions.

As heparin is bound by platelet components (PF4), as a result of which the effect is neutralised, blood taken for coagulation tests and mixed with citrate should be centrifuged and decanted as soon as possible after sampling in order to separate blood cells and blood plasma.

The treating physician decides on the duration of administration.
Regular monitoring of the activated partial thromboplastin time (aPTT) and platelet count are necessary with heparin therapy.

4.3 Contraindications

Heparin Sodium Rovi 5,000 IU/ml must not be used in the following cases:

- Hypersensitivity to the active substance heparin, Benzyl alcohol or to any of the excipients of *Heparin Sodium Rovi 5,000 IU/ml* listed in section 6.1.
- Acute or previous history of heparin-induced allergic thrombocytopenia (type 2).
- Disorders associated with a bleeding diathesis, e.g. thrombocytopenia, coagulopathies, severe hepatic, renal or pancreatic disorders.
- Disorders in which there is a suspected lesion of the vascular system, e.g. gastrointestinal ulcers, hypertension (>105 mmHg diastolic), cerebral haemorrhage, trauma or surgical operations involving the central nervous system (CNS), eye operations, retinopathies, vitreous haemorrhage, aneurysm of the cerebral arteries, infectious endocarditis.
- Threatened miscarriage.
- Spinal anaesthesia, epidural anaesthesia, lumbar puncture.
- Organ lesions associated with a bleeding tendency.

Heparin Sodium Rovi 5,000 IU/ml must not be used in preterm or newborn babies because of the benzyl alcohol content.

4.4 Special warnings and precautions for use

Heparin Sodium Rovi 5,000 IU/ml should not be used in the case of:

- suspected malignancy with a bleeding tendency.
- renal or ureteric calculi.
- chronic alcoholism.

Particularly careful medical monitoring is necessary:

- during pregnancy, especially in the case of prolonged use (see section 4.6).
- in elderly patients, especially in women.
- during concomitant treatment with fibrinolytics or oral anticoagulants, with antiplatelet drugs (e.g. aspirin, ticlopidine, clopidogrel) and/or glycoprotein IIb/IIIa receptor antagonists.
- during concomitant use of medicinal products that increase the serum potassium level. Serum potassium levels should be monitored in at-risk patients (e.g. because of diabetes, impaired renal function or use of medicinal products that increase the serum potassium level).

During treatment with heparin sodium, intramuscular injections should be avoided because of the risk of haematomas.
If thromboembolic complications occur during heparin administration, type 2 heparin-induced thrombocytopenia must be considered in the differential diagnosis and the platelet count monitored.
In infants, children and patients with renal and/or hepatic failure, careful monitoring and testing of coagulation parameters are essential; this also applies to the prophylaxis of thromboembolism (low-dose treatment).
Patients on heparin therapy (of over 22,500 IU/day) should avoid putting themselves at risk of injury.
Heparin can increase and prolong menstrual bleeding. If there is unusually heavy or acyclic bleeding, an organic cause requiring treatment should be excluded by a complementary gynaecological examination.

In isolated cases, the occurrence of spinal and epidural haematomas has been reported in temporal association with spinal or epidural anaesthesia for unfractionated and fractionated low-molecular-weight heparin, especially in the case of intravenous administration or the administration of doses above those recommended for low-dose prophylaxis of thromboembolism (above 15,000 IU unfractionated heparin per day subcutaneously). These haematomas may lead to neurological complications of varying severity and even persistent or permanent paralysis. *Heparin Sodium Rovi 5,000 IU/ml* should therefore be used only after a detailed individual benefit-risk assessment if neuraxial anaesthetic procedures are planned or have already taken place.

According to a recommendation by the German Society of Anaesthesiology and Intensive Care Medicine, a puncture-free interval of 4 hours should be left as a safety precaution between the last administration of *Heparin Sodium Rovi 5,000 IU/ml* at a prophylactic dose (low-dose) and re-insertion or removal of a spinal/epidural catheter. Thereafter, at least 1 hour should be allowed to elapse before the further administration of low-dose *Heparin Sodium Rovi 5,000 IU/ml*.

Patients should be carefully monitored neurologically after the use of a neuraxial anaesthetic procedure, watching particularly for persistent sensory or motor deficits. If a haematoma in the region of the spinal cord is suspected clinically, suitable diagnostic or therapeutic measures should be initiated immediately.

Notes on laboratory investigations:

The platelet count should be checked:
- before the start of heparin administration.
- on the 1st day after the start of heparin administration.
- then regularly every 3-4 days during the first 3 weeks.
- at the end of heparin therapy.

Heparin can distort the results of many laboratory investigations, e.g. the erythrocyte sedimentation rate, erythrocyte fragility and complement fixation tests. Heparin can affect the prothrombin time; this needs to be considered when switching to coumarin derivatives.
The results of thyroid function tests may be distorted during heparin therapy (e.g. false high T_3 and T_4 levels).

***Heparin Sodium Rovi* contains benzyl alcohol**
Benzyl alcohol has been associated with the risk of serious adverse reactions (gasping syndrome) in newborn babies and infants.
In infants (under 3 years of age), the medicinal product should not be used for longer than a week because of accumulation.
Large quantities of benzyl alcohol should be used only with caution and when absolutely necessary because of the risk of accumulation and toxicity (metabolic acidosis), especially in individuals with hepatic or renal impairment and during pregnancy and lactation.

***Heparin Sodium Rovi* contains sodium**
Heparin Sodium Rovi 5,000 IU/ml contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Antiplatelet drugs (aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, dipyridamole in high doses), fibrinolytics, other anticoagulants (coumarin derivatives), oral factor Xa inhibitors (apixaban, rivaroxaban), thrombin inhibitors (bivalirudin, argatroban, dabigatran), hirudin (desirudin), non-steroidal anti-inflammatory drugs (phenylbutazone, indometacin), glycoprotein IIb/IIIa receptor antagonists, high-dose penicillin, dextrans:
Clinically significant increased effect and increased risk of bleeding.

Cytostatics
Increase in the effect of heparin: doxorubicin probably attenuates the effect.

Nitroglycerin, administered intravenously
A clinically significant reduction in the effect of heparin can arise with the intravenous administration of nitroglycerin. After nitroglycerin is stopped, there may be a sharp rise in the aPTT. Close monitoring of the aPTT and adjustment of the heparin dose are necessary during the concomitant infusion of nitroglycerin.

Ascorbic acid, digitalis, tetracyclines, smoking
Inhibition of the effect of heparin.

Medicinal products bound to plasma proteins (e.g. propranolol)
Increase in the effect through displacement from plasma protein binding sites.

Medicinal products that increase the serum potassium level
Medicinal products that increase the serum potassium level must only be used concomitantly with *Heparin Sodium* if there is particularly careful medical monitoring.

Basic medicinal products (tricyclic antidepressants, antihistamines and quinine)
Reciprocal reduction in the effect through salt formation with heparin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Heparin does not cross the placenta. To date, experience in pregnant women has not demonstrated any foetal/neonatal toxicity of heparin. Animal studies have also not shown any evidence of reproductive toxicity (see section 5.3).
There are, however, reports of an increased risk of miscarriages and premature births. Treatment- or disease-induced complications in pregnant women cannot be ruled out. Daily high-dose heparin administration over a period of more than 3 months can increase the risk of osteoporosis in pregnant women.
Epidural anaesthesia is contraindicated during birth in women treated with anticoagulants. Anticoagulant treatment is also contraindicated if there is a bleeding tendency such as with threatened miscarriage (see section 4.3).
If necessary, use of heparin during pregnancy can be considered.

Lactation
Heparin is not excreted in human milk. Heparin can be used during breast-feeding. Daily high-dose administration of heparin over a period of more than 3 months can increase the risk of osteoporosis in breast-feeding women.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions can occur during treatment with *Heparin Sodium Rovi 5,000 IU/ml.*
The frequency data on adverse reactions are based on the following categories:

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	Cannot be estimated from the available data

Blood and lymphatic system disorders

Very common: Depending on the heparin dosage, increased incidence of bleeding, especially from skin, mucous membranes, wounds, gastrointestinal and urogenital tract.

Common: At the start of treatment, type 1 heparin-induced thrombocytopenia not mediated by antibodies (platelet count: 100,000-150,000/µl), without thrombosis.

Rare: Type 2 heparin-induced, antibody-mediated thrombocytopenia (platelet count: <100,000/µl or a rapid fall in the platelet count to <50% of the initial count), with arterial and venous thrombosis or emboli, consumption coagulopathy, skin necrosis, petechiae, melaena. The anticoagulant effect of heparin may be reduced.
In patients without heparin hypersensitivity, the fall in platelet count usually occurs 6-14 days after the start of heparin treatment. In patients with pre-existing heparin hypersensitivity, the fall in platelet count can occur after just a few hours.

Very rare: Type 2 thrombocytopenia can occur after a delay of several weeks after the end of heparin treatment (Spinler S A: New concepts in heparin-induced

thrombocytopenia: Diagnosis and management, J Thromb Thrombolysis 21(1), 17-21, 2006: FDA MedWatch Safety Alert. Heparin Sodium Injection. December 8, 2006).
If type 2 thrombocytopenia occurs, heparin should be stopped immediately. Other treatment measures depend on the nature and severity of symptoms. Further parenteral heparin administration is absolutely contraindicated.

Immune system disorders

Uncommon:	Allergic reactions with symptoms such as nausea, headache, rise in temperature, limb pain, urticaria, vomiting, pruritus, dyspnoea, bronchospasm and a fall in blood pressure. Local and generalised hypersensitivity, including angioedema.
Rare:	Hypersensitivity reactions due to the benzyl alcohol content.
Very rare:	Occurrence of anaphylactic shock, especially in sensitised patients who have previously received heparin.

Endocrine disorders

Rare:	Hypoaldosteronism, associated with hyperkalaemia and metabolic acidosis, especially in patients with renal impairment and diabetes.

Vascular disorders

Very rare:	Vasospasm

Hepatobiliary disorders

Very common:	Elevation of serum transaminases (AST, ALT), gamma-glutamyl transpeptidase (gamma-GT), LDH and lipase.

Reproductive system disorders

Very rare:	Priapism

Skin and subcutaneous tissue disorders

Uncommon:	Transient alopecia, skin necrosis.

Musculoskeletal and connective tissue disorders

Not known:	Osteoporosis may develop after prolonged use (months), mostly when higher doses are used and especially in patients with a predisposition to it.

General disorders and administration site conditions

Common:	Local tissue reactions at the injection site (induration, redness, discoloration and small haematomas).
Very rare:	Calcinosis at the injection site, mainly in patients with severe kidney failure.

Benzyl alcohol can cause allergic reactions.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

Additionally, you should also report to Kamada Ltd. to email address:
pharmacovigilance@kamada.com

4.9 Overdose

a) Symptoms of an overdose
Bleeding, in most cases from the skin and mucous membranes, wounds, gastrointestinal and urogenital tract (epistaxis [nosebleed], haematuria, melaena, haematomas, petechiae). A fall in blood pressure, decrease in haematocrit or other symptoms may be signs of occult bleeding.

b) Treatment of overdose
Mild bleeding
Reduce the heparin dose if necessary.

Moderate non–life-threatening bleeding
Suspend the heparin therapy.

More serious, life-threatening bleeding
Reverse the effect of heparin with protamine after excluding other causes of bleeding (e.g. consumption coagulopathy, factor deficiency).
Protamine should be administered only in the case of life-threatening bleeding, as there is an increased risk of thromboembolic complications once the heparin has been completely neutralised. The patient must be monitored and treatment continued in intensive care.
The antidote protamine is an arginine-rich protein which is usually used in the form of a chloride or sulphate. As a general rule, 1 mg of protamine neutralises the effect of about 100 IU of heparin (1 IU of protamine neutralises 1 IU of heparin). The half-life of heparin and the route of administration need to be borne in mind for the treatment, i.e.

- 90 minutes after intravenous heparin administration, only 50% of the calculated protamine dose should be given.
- 3 hours after intravenous administration only 25% should be given.

In the event of over-titration, protamine can itself cause an increased bleeding tendency through various mechanisms. If protamine is injected intravenously too quickly, there may be a fall in blood pressure, bradycardia, dyspnoea and a feeling of oppression. Protamine is eliminated from the bloodstream more rapidly than heparin. The neutralisation effect must therefore be monitored by regular assays of the activated partial thromboplastin time (aPTT). Heparin is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agent
ATC code: B01AB01

Heparin is a mucopolysaccharide polysulphate ester and consists of glucosamine-N-sulphuric acid and sulphate esters of glucuronic acid, which are linked to each other through glycosidic bonds.
Because of its strong negative charge, heparin forms complexes with certain proteins and thereby alters their biological properties. This applies above all to antithrombin III (ATIII), which experiences an approximately 700-fold increase in activity as a result of complex formation with heparin.
Activated ATIII brings about inhibition of serine proteases, which include the clotting factors XIIa, XIa, Xa, VIIa and IIa. Factor VIIa is relatively weakly inhibited by the heparin-ATIII complex and factor IIa (thrombin) is inhibited by it to a particularly marked extent. Even low heparin doses accelerate inhibition of factor IIa (thrombin) and factor Xa by ATIII. This explains the prophylactic effect of low-dose heparin for the prevention of thromboembolic disorders. The anticoagulant effect primarily depends on the amount of ATIII available and the fibrinogen concentration; some substances contained in platelets (platelet factor 4) likewise neutralise the effect of heparin. In addition, high heparin doses inactivate any excess thrombin and thus prevent fibrin from arising from fibrinogen. Heparin also influences platelet functions.

5.2 Pharmacokinetic properties

Heparin can be administered subcutaneously or intravenously. Heparin is not absorbed from the intestine because of its molecule size and negative surface charge; absorption by inhalation is possible. The effect of heparin sets in immediately after intravenous administration, and within 20-30 minutes after subcutaneous injection. Bioavailability after subcutaneous injection varies between individuals. After subcutaneous administration of 5,000 IU of heparin twice daily, plasma levels of between 0.02 IU/ml and 0.8 IU/ml have been measured. The half-life varies a great deal between individuals; the mean half-life is stated as 90-120 minutes and depends on the dose and on liver and kidney function, as well as co-morbidity. Heparin is highly bound to plasma proteins (LDL, globulins [especially ATIII] and fibrinogen); the volume of distribution in adults is stated as being about 0.07 l/kg. After parenteral administration, heparin is eliminated from the bloodstream by uptake into the reticuloendothelial system, by cleavage in the liver (heparinases) and by excretion in urine mainly as depolymerised, inactivated heparin. Heparin excretion takes place by both glomerular filtration and tubular secretion.

5.3 Preclinical safety data

Animal studies revealed only effects (osteoporosis and bleeding) that are already described in section 4.8. In vitro and in vivo tests for genotoxic effects did not show any evidence of a mutagenic potential. Studies of carcinogenic potential have not been conducted. Animal studies have not produced any evidence of teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, sodium chloride, sodium hydroxide, water for injection.

6.2 Incompatibilities

Heparin must not be drawn up into a syringe or administered in an infusion along with other medicinal products because of the danger of physical and chemical incompatibilities.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Once the vial has been opened, administer the product immediately.

6.4 Special precautions for storage

Do not store over 30º C.

6.5 Nature and contents of container

Type I glass vials, with bromobutyl rubber stopper and aluminium protective capsule.

5 ml vials in packs of 50 vials.

6.6 Special precautions for disposal and other handling

Administration of the subcutaneous injection
The injection should be administered with a fine injection needle held perpendicular to the body axis, into a raised fold of abdominal skin or on the anterior aspect of the thigh; the injection must be strictly subcutaneous.
Any drops adhering to the injection needle should be removed before the injection, as

introducing heparin sodium into the injection channel can result in superficial bruising and in rare cases local allergic irritation.

Only use if the solution is clear and colourless, and free of visible particles. Any unused medicinal product or waste materials should be disposed of in accordance with local requirements.

7. LICENCE HOLDER AND MANUFACTURER

Licence holder:
Kamada Ltd., Beit Kama, MP NEGEV 8532500, Israel

Manufacturer:
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Julián Camarillo, 35 - 28037 Madrid - Spain

8. REGISTRATION NUMBER

162-77-35345

Revised in October 2024.