SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Heparin PANPHARMA
5,000 IU/1 ml solution for injection
25,000 IU/5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution for injection contains:
Heparin sodium (porcine intestinal mucosa) 5,000 IU
Each ampoule with 1 ml contains Heparin sodium 5,000 IU
Each ampoule with 5 ml contains Heparin sodium 25,000 IU

Other ingredients with known effect: Benzyl alcohol and sodium
1 ml solution for injection contains 10 mg benzyl alcohol and 5,4 mg sodium

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to slightly yellowish, aqueous solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

– Prophylaxis for thrombo-embolic diseases
– in the context of treatment of venous and arterial thromboembolic diseases (including early treatment of heart attack as well as unstable angina pectoris).
– for anticoagulation for treatment or operation with extracorporeal circulation (e.g. heart-lung machine, haemodialysis)

4.2 Posology and method of administration

Posology
Sodium heparin dosage must be individually determined

Dosage depends upon clotting values (see Section 4.4), the type and course of the disease, patient response, side-effects, weight and age of the patient. Varying heparin sensitivity and a possible change in heparin tolerance must be considered over the course of treatment.

Thromboembolic prophylaxis ("low-dose" treatment)

Subcutaneous injection is recommended for thromboembolic prophylaxis.
General dosage recommendations for thromboembolic prophylaxis:

Pre- and post-operative thromboembolic prophylaxis
Pre-operatively 5,000-7,500 IU subcutaneous, about two hours before the operation. Post-operatively, depending upon thrombosis risk; as a rule, 5,000 IU subcutaneously every 8 to 12 hours or 7,500 IU

subcutaneously every 12 hours until the patient is mobilized or until there is sufficient efficacy of vitamin K antagonists. Laboratory monitoring (clotting values) for dose adjustment may be necessary in individual cases.

Prophylaxis in non-operative medicine
(e.g. when bedridden for a longer period of time, patients have a higher thrombosis tendency, diseases with higher risk of thrombosis)
Depending upon the thrombosis risk, as a rule 5,000 IU subcutaneously every 8 to 12 hours or 7,500 IU subcutaneously every 12 hours.
Dosage must be adjusted according to the risk of thrombi and the degree of activity of the coagulation system, and can be determined by coagulation monitoring.

In the context of therapy of venous and arterial thromboembolic diseases

With existing clots in blood vessels, continuous IV administration is recommended.

Dosage for adults
In general, start with 5,000 IU sodium heparin as an IV bolus, followed by continuous infusion with 1,000 IU sodium heparin per hour using a perfusor.

Dose for children
Initially, 50 IU per kg body weight, then 20 IU per kg body weight per hour.

If an intravenous continuous infusion is not possible, as an alternative, use subcutaneous treatment (distributed over 2-3 individual doses) with close treatment monitoring (e.g. 10,000-12,500 IU sodium heparin every 12 hours)

Treatment monitoring and dose adjustment are generally made using activated partial thromboplastin time (aPTT), which should be 1.5 to 2.5 times the normal value. Monitoring of aPTT is recommended with continuous IV heparin administration 1-2 hours, 6 hours, 12 hours and 24 hours after the start of treatment, and with subcutaneous application, 6 hours after administration of the 2nd dose.

Treatment of venous thromboemboli
One should start with 5,000 IU sodium heparin IV as a bolus, followed by an IV infusion of, as a rule, 1,000 IU of sodium heparin per hour. Dosage should be adjusted as per aPTT values, whereby a lengthening of the aPTT to 1.5 to 2.5 times the starting value should be achieved (if possible, within the first 24 hours).
Treatment should be carried out over a minimum of four days, or continued until a sufficient oral anticoagulation is achieved.

For unstable Angina pectoris or non-Q wave infarction:
In general, administer 5,000 IU sodium heparin as a bolus, followed by a continuous infusion of 1,000 IU/hour. The dose should be set by aPTT values, which should be lengthened to 1.5 to 2.5 times the normal value.
Sodium heparin should be given for at least 48 hours.

As accompanying treatment of thrombolysis with fibrin-specific thrombolytic agents (e.g. r-tPA) for treatment of acute myocardial infarction:
Initially 5,000 IU sodium heparin IV as a bolus, followed by an intravenous infusion of 1,000 IU per hour.
The infusion should be set in accordance with aPTT levels with a lengthening of the starting value by 1.5 to 2.5 times. Sodium heparin should be given over 48 hours.
For thrombolysis with non-fibrin-specific thrombolytic agents (e.g. streptokinase), 12,500 IU of sodium heparin can be administered subcutaneously every 12 hours, starting 4 hours after thrombolysis.
The exact dosage of concomitant heparin treatment is determined by the type of thrombolytic agent

and is to be undertaken in accordance with the information given for individual thrombolytic agents.

Anticoagulation for treatment or operation with extracorporeal circulation

Haemodialysis:
Dosage must be adjusted according to the coagulation tests and the type of machine.

Heart-lung machine:
The dosage depends upon the type of heart-lung machine and the duration of the operation, and must be handled on an individual basis.

Method of administration

For subcutaneous and intravenous administration, as an injection, or diluted as an intravenous infusion.

Subcutaneous injection
The injection should be performed with a fine injection needle, perpendicular to the body axis, in a lifted abdominal fold or on the front of the thigh; the injection must be done subcutaneously. Any drops on the injection needle must be removed before injection, as putting sodium heparin in the injection channel can lead to surface bruising or, in rare cases, to allergic irritation.

Infusion:
Heparin PANPHARMA can be diluted for IV infusion with the solutions listed in Section 6.6.

To reduce lymph flow disruptions, Heparin PANPHARMA should be applied to the upper arm in patients who having their lymph nodes removed in the abdominal or urogenital area.

4.3 Contraindications

Heparin PANPHARMA must not be used:
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- if there is a history of known heparin-induced thrombocytopenia type II or clinical suspicion of heparin-induced thrombocytopenia type II under heparin treatment (e.g. with the development of thrombocytopenia under heparin, and/or occurrence of new arterial and/or venous thromboembolic complications under heparin treatment)
- with diseases associated with a haemorrhagic diathesis, such as thrombocytopenia, coagulopathies, severe liver, kidney or pancreatic diseases
- with diseases which can occur with suspicion of a lesion in the vascular system, such as stomach and/or intestinal ulcer, high blood pressure (greater than 105 mmHg diastolic), cerebral haemorrhage, trauma or surgical procedure on the central nervous system, eye operations, retinopathies, vitreous haemorrhaging, cerebral arterial aneurysm, infectious endocarditis
- Abortus imminiens
- Spinal anaesthesia, epidural anaesthesia, lumbar puncture
- Organ lesions associated with bleeding tendencies
- Newborns, especially premature babies, due to the benzyl alcohol content

4.4 Special warnings and precautions for use

Heparin PANPHARMA must not be used if there is:
- suspicion of a malignant tumour with a bleeding tendency
- kidney and urinary tract stones
- chronic alcoholism

Particularly careful monitoring by a doctor is necessary

– during pregnancy, especially for longer application
– in older patients, particularly in women,
– with concomitant treatment with fibrinolytic agents or oral anticoagulants, with drugs which impact platelet function (such as aspirin, ticlopidine, clopidogrel) and/or, glycoprotein IIb/IIIa receptor antagonists.
– with concomitant use of medicines which increase blood potassium levels Potassium levels in blood should be tested in relevant at-risk patients, such as patients with (Diabetes mellitus. Patients with reduced kidney function or who take medicines which increase potassium concentration in blood should be checked.

During treatment with heparin, IM injections should be avoided due to the danger of bruising.

If thromboembolic complications occur while being treated with heparin, a differential diagnosis of heparin-induced thrombocytopenia type II must be suspected, and platelet count monitored.

In infants, children and patients with kidney and/or liver failure, careful monitoring and control of clotting values is necessary; this also applies for thromboembolic prophylaxis ("low-dose" treatment).

Patients under heparin treatment (over 22,500 IU/day) should avoid injury hazards.

Heparin can increase and lengthen the period of menstrual bleeding. With unusually strong and irregular menstrual bleeding, organic causes must be excluded with a gynaecological examination.

Instructions on laboratory diagnostic tests

Regular monitoring of clotting values (aPTT) as well as platelet values are required when administering heparin.
Regular monitoring of platelet counts must be carried out in order to recognize a reduction in the number of platelets caused by heparin
– before starting heparin administration
– on the first day after starting heparin treatment
– Finally every 3-4 days during the first three weeks of administration
– at the end of heparin treatment

If heparin is, above all, used in higher doses over several months, increased bone fragility (osteoporosis) can occur, especially in patients who have this predisposition.

Benzyl alcohol can create appearance of toxicity and hypersensitivity reactions. (see also Section 4.8)

Heparin can falsify the results of many laboratory tests, such as blood reduction speed, erythrocyte resistance and complement binding tests.
Heparin can influence prothrombin time; this must be noted when setting warfarin (coumarin) derivative dosages.
The results of thyroid function tests can be falsified under heparin treatment (such as falsely-high T_3 and T_4 values).

This medicinal product contains 27 mg sodium per 5 ml, equivalent to 1,35% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 10 mg benzyl alcohol in each 1 ml solution for injection. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.

Do not use for more than a week in young children (less than 3 years old), due to accumulation.

High volumes should be used with caution and only if necessary, especially in subjects with liver or

kidney impairment and during or during breast-feeding because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been observed with this medication:

- Platelet aggregation inhibitors (ASA, ticopidine, clopidogrel, dipyridamo in higher doses, fibrinolytic agents, other anticoagulants (warfarin derivatives), non-steroidal anti-inflammatory agents (phenylbutazone, indometacin, sulfinpyrazone), glycoprotein IIb/IIIa receptor antagonists, penicillin in higher doses and dextrane:

Clinically important enhanced effect and increased risk of blood clots.

- *Cytostatic agents:*

These can increase heparin effects; Doxorubicin may weaken these effects

- *Nitroglycerin (IV)*

Clinically significant reduction in efficacy: After stopping the use of nitroglycerin, there can be a sudden increase in aPTT. Close monitoring of aPTT and dose adjustment if there is concomitant infusion of nitroglycerin is necessary.

- *Ascorbic acid, antihistamines, digitalis, tetracycline, nicotine abuse:*

Possible prevention of heparin effectiveness

- *Also, medications which are bound to plasma proteins (e.g. Propranolol):*

An increase in efficacy can occur with displacement of plasma protein binding

- *Drugs which increase blood potassium levels:*

May only be taken with close medical supervision concomitantly with Heparin PANPHARMA.

- *Basic medications (such as certain drugs to treat mental diseases (tricyclic psycho-pharmaceutical agents), antihistamines and quinine)*

Counteracting efficacy reduction through the formation of salt with heparin.

4.6 Pregnancy and breast feeding

Pregnancy

Heparin does not pass through the placenta. There are no reports to date that show that heparin can lead to birth defects when taken during pregnancy. Animal experiments have shown no evidence of damage to fertility (see Section 5.3).

There are reports, however, of an increased risk of miscarriages and premature birth. Treatment or disease-related complications cannot be excluded during pregnancy.

Daily high-dose heparin over a period of more than three months could increase the risk of osteoporosis in pregnant women. Heparin should not be administered in these cases for longer than three months.

Epidural anaesthesia is contraindicated during the birth process. Also, clot-preventing treatment is contraindicated if there is a tendency to bleed, such as with a threatened miscarriage (see Section 4.3).

Breast feeding

Heparin is not transferred into mother's milk. Daily high-dose heparin over a period of more than three months could increase the risk of osteoporosis in nursing women.

4.7 Effects on ability to drive and use machines

Heparin does negligibly or not affect the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions may occur when being treated with Heparin PANPHARMA

The following frequency of occurrence categories are used:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10000 to < 1/1000)
Very rare (< 1/10000)
Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very common:	Depending upon heparin dosage, multiple occurrences of bleeding, especially of the skin, mucous membranes, wounds, gastrointestinal and urinary tracts.
Common:	At the start of treatment, thrombocytopenia type I without antibody participation (platelet count: 100,000-150,000/micro litre) without thrombosis.
Rare:	Massive reduction in platelet count (antibody-mediated thrombocytopenia type II with blood platelet counts of less than 100,000 per micro litre or fast reduction in blood platelet count to less than 50% of the starting value), with thromboses in the arteries or veins or vascular closures due to blood clots, uptake of clotting factors, skin injuries (necroses), petechiae, black stools. The clot-preventing effect of heparin can be reduced.

In patients who are hypersensitive to heparin, the reduction in platelet counts starts for the most part 6 to 14 days after the start of heparin treatment. In patients with already-existing hypersensitivity to heparin, the reduction in blood platelet counts can begin after only a few hours.

Very rare:	Type II thrombocytopenia occurs only 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]

As soon as type II thrombocytopenia occurs, immediately stop the administration of heparin. Further treatment modalities depend upon the type and severity of the symptoms.
Further parenteral heparin administration is absolutely contraindicated.

Immune system disorders

Uncommon:	Allergic reactions with symptoms such as: nausea, headaches, increase in temperature, joint pains, urticaria, vomiting, pruritus, dyspnoea, bronchospasms) and a fall in blood pressure. Local and generalized hypersensitivity, including angio-oedema, temporary alopecia, skin necroses
Rare:	Hypersensitivity reactions to benzyl alcohol.
Very rare:	Occurrence of an anaphylactic shock, especially in sensitized patients who have received heparin earlier.

Endocrine disorders

Rare:	Hypoaldosteronism, connected with hyperkalemia and metabolic acidosis,

especially in patients with limitations in kidney function and Diabetes mellitus.

Vascular disorders

Very rare: Vasospasms

Hepatobiliary disorders

Very common: Increase in serum transaminases (GOT, GPT,) gamma GT as well as LDH and lipase.

Reproductive system and breast disorders

Very rare: Priapism

Skin and subcutaneous tissue disorders

Very rare: Temporary alopecia, skin necroses

Musculoskeletal and connective tissue disorders

If heparin is, above all, used in higher doses over several months, increased bone fragility (osteoporosis) can occur, especially in patients who have this predisposition.

General disorders and administration site conditions

Common: Tissue reactions at the injection site (hardening, reddening, discolouration and small bruises)
Very rare: Calcification of the subcutaneous tissue at the injection site, mainly in patients with severe kidney failure

Benzyl alcohol may 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. Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system according to local regulations.

4.9 Overdose

Symptoms of an overdose

Bleeding, mostly from the skin and mucous membranes, wounds, gastrointestinal and urogenital tracts (epistaxis, haematuria, melena, haematoma, petichiae). Fall in blood pressure, reduction in the haematocrit or other symptoms can be signs of occult bleeding.

Treatment of an overdose

Slight bleeding
If required, reduce the heparin dose.

Moderate, not threatening bleeding
Interrupt heparin treatment.

More serious, life-threatening bleeding

Stop the heparin effect with protamine after exclusion of other causes of bleeding (such as use of coagulopathy, missing factors).

Protamine should only be administered if there is life-threatening bleeding; a complete neutralization of heparin can lead to an increased risk of thromboembolic complications. The patient must be monitored and cared for in an ICU environment.

The antidote, protamine, is an arginine-rich protein which is usually given as a sulphate or chloride. As a rule, 1 mg protamine neutralizes about 100 IU of heparin (1 IU protamine neutralizes 1 IU heparin). For treatment, the half-life of heparin and type of application must be considered, i.e.

– 90 minutes after IV heparin application, only 50% of the calculated protamine volume is to be given.
– Three hours after IV administration, only 25%.

If there is an over titration, protamine can cause increased tendency to bleeding through various mechanisms. If protamine is injected IV too quickly, it can lead to a fall in blood pressure, bradycardia, dyspnoea and a feeling of tightness. Protamine is more quickly eliminated from the blood than heparin. The effect of the neutralization must therefore be monitored with regular determination of the aPTT.

Heparin cannot be dialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antithrombotic medicine, heparin group
ATC code B01AB01

Heparin is a mucopolysaccharide polysulphuric acid ester and consists of glucosamine-N-sulphuric acid and sulphuric acid esters of gluconic acid, which are glycolically interconnected.

Heparin forms specific protein complexes and therefore changes their biological properties due to its strong negative charge. This especially affects antithrombin (AT), which, through its compounding with heparin, increases activity by about 700 times.

Activated AT causes a prevention of serum proteases, to which belong the clotting factors XIIa, XIa, Xa, VIIa and IIa. Thus FVIIa is relatively weak, and FIIa (thrombin) is especially strongly inhibited by the heparin-AT complex. Even low heparin doses accelerate the inhibition by AT of FIIa (thrombin and FXa. This explains the prophylactic effect of low-dose heparin to prevent thromboembolic diseases. The clot-inhibition effect depends above all on the available amount of AT and the fibrinogen concentration: certain platelet contents (platelet factor 4) also neutralize heparin. High heparin doses additionally inactivate an over-abundant amount of formed thrombin, and inhibit the creation of fibrin from fibrinogen. Heparin also influences platelet function.

5.2 Pharmacokinetic properties

Heparin can be administered subcutaneously or intravenously. Due to its molecular size and negative surface charge, heparin is not resorbed by the intestines; it can be inhaled.

The effect of heparin after IV administration starts immediately; after subcutaneous injection, it takes effect in 20 to 30 minutes.

The bioavailability is 100%.

The inter-individual half-life is given as 90- to 120 minutes, and depends upon the dose and the

function of the liver and kidneys as well as co-morbidities.

Heparin is bound to a great degree to plasma proteins (LDL, globulines [especially AT] and fibrinogen), the distribution volume in adults is given as about 0.07 l/kg.

After parenteral administration, heparin is taken up from the blood into the reticuloendothelial system, by splitting in the liver (heparinases), and through excretion through the urine, primarily as depolymerized, inactivated heparin. Heparin excretion takes place as well through glomerular filtration as well as through tubular secretion.

5.3 Preclinical safety data

In animal experiments, effects occurred which are described in Section 4.8 (osteoporosis and bleeding). In-vitro and in-vivo studies on genotoxic effects have shown no evidence of mutagenic potential. Experiments for tumour-producing potential have not been carried out. Animal experiments have shown no evidence of fertility-damaging influences (see Section 4.6)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (preservative), sodium chloride, water for injections.

6.2 Incompatibilities

Due to the risk of physical-chemical incompatibilities, heparin may not be drawn together with other medications into a syringe, or jointly administered in an infusion.

6.3 Shelf life

Unopened
5 years

Shelf life after in-use
A vial can be used up to 28 days after the first in-use, if the removal has taken place under controlled and validated aseptic conditions. The date of the in-use should be marked on the label.

Shelf life after reconstitution
Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C ± 2 °C)
From microbiological point of view, the product 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 24h at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

There are no specific storage conditions required for this medicinal product.

Storage conditions after in-use and reconstitution, see section 6.3.

6.5 Nature and contents of container

Clear glass ampoules with a filling volume of 1 ml.
Pack of 10 ampoules of 1 ml of solution for injection.

Vial made of clear glass with a rubber stopper, capacity of 5 ml
Pack of 5 vials of 5 ml of solution for injection.
Pack of 25 vials of 5 ml of solution for injection.

6.6 Special precautions for disposal

See Section 6.3 for storage after in-use.

Heparin PANPHARMA can be diluted for IV infusion with the following solutions:
- Sodium chloride: 9 mg/ml IV solution
- Glucose: 50 mg/ml IV solution
- Glucose: 100 mg/ml IV solution
- Ringer solution for infusion

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

7. MARKETING AUTHORISATION HOLDER

PANPHARMA GmbH
Bunsenstrasse 4
22946 Trittau
Germany

8. MARKETING AUTHORIZATION NUMBER

08254/08116/REN/2021

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

May 25, 2017 / December 22, 2022

10. DATE OF REVISION OF THE TEXT

June 2020

11. PRESCRIPTION STATUS/ PHARMACY ONLY

Prescription only