SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT

HEPARIN Sodium 1000 IU/ml ampoule, Solution for infusion*

* Pump-Hep for branded product

2  QUALITATIVE AND QUANTITATIVE COMPOSITION

Heparin sodium 1000 IU/ml

3  PHARMACEUTICAL FORM

Solution for infusion.

4  CLINICAL PARTICULARS

4.1  Therapeutic indications

Treatment of thrombo-embolic disorders such as: deep vein thrombosis, acute arterial embolism or thrombosis, thrombophlebitis, pulmonary embolism, fat embolism.
Prevention of clotting in the extracorporeal circuit during haemodialysis.

4.2  Posology and method of administration

Treatment of thrombo-embolic disorders: This product may be used when heparin is being administered intravenously as an alternative to diluting heparin taken from multidose vials.

Dosage adjustment: It is recommended that dosages be adjusted to maintain a thrombin clotting time, whole blood clotting time or activated partial thromboplastin time 1.5 to 2 times that of control on blood withdrawn 4-6 hours after commencement of infusion and at similar intervals until the patient is stabilised.
**Dosage in the elderly:** Lower dosages may be required, however, standard dosages should be given initially and then subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

**Pregnancy:** See Section 4.6, Pregnancy and Lactation. If treatment is considered appropriate, standard dosages should be given initially. Intermittent intravenous injections are not advised. Subsequent dosages and/or dosage intervals should be individually adjusted according to changes in thrombin clotting time, whole blood clotting time and/or activated partial thromboplastin time.

**Prevention of clotting during haemodialysis:**
An initial bolus dose should be given, followed by a continuous intravenous infusion.

**Adults:**
Initially: 1,000 - 5,000 IU.
Maintenance: 1,000 - 2,000 IU per hour, adjusted to maintain clotting time > 40 minutes.

Method of administration
500 IU/kg bodyweight daily or 5,000 - 10,000 IU every 4 hours as a continuous infusion in sodium chloride injection or dextrose injection. The dose should be individually adjusted according to coagulation tests.

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4.3 **Contraindications**

Known hypersensitivity to constituents.

Current or history of heparin-induced thrombocytopenia.

Generalised or local haemorrhagic tendency, including uncontrolled severe hypertension, severe liver insufficiency, active peptic ulcer, acute or subacute septic endocarditis, intracranial haemorrhage or injuries and operations on the central nervous system, eyes and ears, and in women with abortus imminens.

An epidural anaesthesia during birth in pregnant women treated with heparin is contraindicated (see Section 4.6).

In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contra-indicated because the use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis.
4.4 Special warnings and precautions for use

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

Care should be taken when heparin is administered to patients with increased risk of bleeding complications, hypertension, renal or hepatic insufficiency.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Drugs affecting platelet function or the coagulation system should in general not be given concomitantly with heparin (see Section 4.5).

In patients undergoing peridural or spinal anaesthesia or spinal puncture, the prophylactic use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. The risk is increased by the use of a peridural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants, and by traumatic or repeated puncture.

In decision making on the interval between the last administration of heparin at prophylactic doses and the placement or removal of a peridural or spinal catheter, the product characteristics and the patient profile should be taken into account. Subsequent dose should not take place before at least four hours have elapsed. Re-administration should be delayed until the surgical procedure is completed.

Should a physician decide to administer anti-coagulation in the context of peridural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits and bowel or bladder dysfunction. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these.

Heparin should not be administered by intramuscular injection due to the risk of haematoma.

Due to increased bleeding risk, care should be taken when giving concomitant intramuscular injections, lumbar puncture and similar procedures.

As there is a risk of antibody-mediated heparin-induced thrombocytopenia, platelet counts should be measured in patients receiving heparin treatment for longer than 5 days and the treatment should be stopped immediately in those who develop thrombocytopenia.
Heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombosis can occur up to several weeks after discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

4.5 Interaction with other medicinal products and other forms of interaction

The anticoagulant effect of heparin may be enhanced by concomitant medication with other drugs affecting platelet function or the coagulation system, e.g. platelet aggregation inhibitors, thrombolytic agents, salicylates, non-steroidal anti-inflammatory drugs, vitamin K antagonists, dextrans, activated protein C. Where such combination cannot be avoided, careful clinical and biological monitoring is required.

Combined use with ACE inhibitors or angiotensin II antagonists may increase the risk of hyperkalaemia.

Use of glyceryl trinitrate infusion may reduce the anticoagulant effect of heparin.

4.6 Fertility, pregnancy and lactation

Because of the known haemorrhagic effect, heparin should be used with caution in pregnant women and only if the benefits outweigh the risks according to the physician’s judgement. Precaution is particularly required because of uteroplacental haemorrhage, especially at the time of delivery. If epidural anaesthesia is envisaged, heparin treatment should be suspended, whenever possible.

The use of heparin in women with abortus imminens is contraindicated (see Section 4.3).

Heparin does not cross the placental barrier and is not excreted in breast milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects
Frequency estimate: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequently reported undesirable effects are bleeding events, reversible increase in liver enzymes, reversible thrombocytopenia and various skin reactions. Isolated reports of generalised allergic reactions, skin necrosis and priapism have been reported.

- **Blood and lymphatic system disorders**
  Heparin can cause thrombocytopenia either through a direct effect or through an immune effect producing a platelet-aggregating antibody (see Section 4.4). Reversible after drug withdrawal.
  - **Common:** Thrombocytopenia type I
  - **Rare:** Thrombocytopenia type II, probably of an immunoallergic nature (see section 4.4)
  In some cases thrombocytopenia type II has been accompanied by venous or arterial thrombi.

- **Immune system disorders**
  - **Rare:** Allergic reactions of all types and severities, with various manifestations
  - **Very rare:** Anaphylactoid reactions and anaphylactic shock

- **Metabolism and nutrition disorders**
  - **Rare:** Hypoaldosteronism. Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see Section 4.4).

- **Vascular disorders**
  - **Common:** Haemorrhage
    Haemorrhages may affect any organ, particularly in connection with high doses.
    In some cases haemorrhage has resulted in death or permanent disability.

  Very rare cases of epidural and spinal haematoma have been reported in patients receiving heparin for prophylaxis undergoing spinal or epidural anaesthesia or spinal puncture (see Section 4.4).

- **Hepatobiliary disorders**
  - **Common:** Raised transaminases, gamma-GT, LDH and lipase levels. They are reversible after drug withdrawal.

- **Skin and subcutaneous tissue disorder**
  - **Uncommon:** Rash (various types of rash such as erythematous and maculopapular), urticaria, pruritus.
  - **Rare:** Skin necrosis. If this occurs treatment must be withdrawn immediately.
    One case of erythema multiforme was also reported.
- **Musculoskeletal and connective tissue disorders**
  Uncommon: Osteoporosis has been reported in connection with long-term heparin treatment.
- **Reproductive system and breast disorders**
  Very rare: Priapism
- **General disorders and administration site conditions**
  Common: Injection site reactions; local irritation may occur when injected subcutaneously

**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 the yellow card scheme at www.mhra.gov.uk/yellowcard

4.9 **Overdose**

Bleeding is the main sign of overdose with heparin. As heparin is eliminated quickly, a discontinuation of treatment is sufficient in case of minor haemorrhages. In case of severe haemorrhages heparin may be neutralised with protamine sulphate injected slowly intravenously. One mg of protamine sulphate neutralises approximately 100 IU of heparin. Nevertheless, the required protamine sulphate dose varies according to the time of heparin administration and the dose administered.

It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. A single dose of protamine sulphate should never exceed 50 mg. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea and transitory flushing, but these may be avoided or diminished by slow and careful administration.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in vivo and in vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and Factor X.
5.2 Pharmacokinetic properties

The anticoagulant effect of heparin after intravenous infusion becomes apparent immediately.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium citrate, water for injections.

6.2 Incompatibilities

Heparin has been reported to be incompatible in aqueous solutions with certain substances, e.g. some antibiotics, hydrocortisone, phenothiazines, narcotic analgesics and some antihistamines.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Ph. Eur. Type I glass ampoules.
10 x 5ml ampoules, 50 x 5ml ampoules
10 x 10ml ampoules, 50 x 10ml ampoules
10 x 20ml ampoules, 50 x 20ml ampoules

6.6 Special precautions for disposal

Any portion of the contents not used at once should be discarded.

7 MARKETING AUTHORISATION HOLDER

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Wellingborough
Northamptonshire
NN8 6GT

8 MARKETING AUTHORISATION NUMBER(S)

PL 20417/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

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10 DATE OF REVISION OF THE TEXT

28/02/2016