Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Protamine sulphate LEO Pharma 1400 anti-heparin IU/ml solution for injection and infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Protamine sulphate 1400 anti-heparin IU/ml (corresponds to 10 mg/ml) extracted from the sperm of *Onchorhynchus keta* (salmon).

1 ml contains 1400 anti-heparin IU protamine sulphate (10 mg)
5 ml contains 7000 anti-heparin IU protamine sulphate (50 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion.
Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Protamine sulphate can be used
- in the treatment of overdosage or haemorrhage during heparin or Low Molecular Weight Heparin (LMWH) therapy
- to counteract the anticoagulant effects of heparin or LMWH before emergency surgery.
- to reverse the anticoagulant effects of heparin in cardiopulmonary bypass procedures.

4.2 Posology and method of administration

Posology

Protamine sulphate is administered as a slow intravenous injection over a period of about 10 minutes or as a constant, slow intravenous infusion. The largest single injection (bolus dose) should not exceed 5 ml (7000 anti-heparin IU/50 mg protamine sulphate). Ideally the dose should be guided by blood coagulation studies. The activated partial thromboplastin time (APTT) activated clotting time (ACT), anti Xa and bedside protamine neutralisation test are adequate for this purpose. Coagulation tests are usually performed 5 to 15 minutes after protamine sulphate administration. Further doses may be needed because protamine sulphate is cleared from the blood more rapidly than heparin and especially LMWH. The prolonged absorption after subcutaneous administration of heparin or LMWH might also indicate that repeated doses must be given.

Neutralisation of Heparin:
1 ml of Protamine sulphate LEO Pharma (10 mg protamine sulphate) will neutralise approximately 1400 IU of heparin. As heparin has a relatively short half-life when given intravenously (30 minutes - 2 hours), the dose of protamine sulphate should be adjusted on the basis of the time elapsed since the intravenous administration of heparin was discontinued. The dose of protamine sulphate in relation to the administered amount of heparin should be reduced if more than 15 minutes have elapsed since intravenous injection of heparin has stopped.

Neutralisation of Low Molecular Weight Heparin (LMWH):
A dose of 1 ml of Protamine sulphate LEO Pharma (10 mg protamine sulphate) per 1000 anti Xa IU LMWH is usually recommended. Protamine sulphate neutralises the various LMWHs to a different extent; therefore for each LMWH the manufacturer’s own guidelines should be consulted in case of an overdose (see section 5.1).
Protamine sulphate is only partly able to neutralize the anti-Xa activity made by LMWH, and the neutralization will not

be more effective if higher doses of protamine sulphate than those recommended are administered.
The risk that the neutralization is incomplete with only one injection of protamine sulphate exists with neutralization of subcutaneously administered LMWH. The absorption phase from the injection site will then lead to additional LMWH being added to the circulation (a so-called 'depot effect'). In these cases, repeat administrations of protamine sulphate may be necessary or a continuous, slow, intravenous infusion may be employed. The half-life of LMWHs should also be borne in mind when estimating the dose of protamine sulphate required in relation to the time which has elapsed since the last LMWH dose.

Cardiopulmonary bypass procedures:
It is recommended that doses of protamine sulphate be guided by blood coagulation studies. The activated partial thromboplastin time (APTT), activated clotting time (ACT), anti Xa and bedside protamine neutralisation test are adequate for this purpose. Coagulation tests are usually performed 5 to 15 minutes after protamine sulphate administration. Generally, a dose of 0.1 ml to 0.2 ml (1 – 2 mg) of Protamine sulphate LEO Pharma is administered intravenously for each 100 units of heparin given.

Paediatric population
The safety and efficacy of protamine sulphate in children below 18 years have not been established, see section 4.8

Patients with renal and hepatic impairment
No information is available with regard to the use of protamine sulphate in patients with renal or hepatic insufficiency.

Elderly patients
No information is available with regard to the use of protamine sulphate in the elderly.

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Administration of protamine sulphate can cause anaphylactic reactions and therefore facilities for resuscitation and treatment of shock should be available.

Administration of protamine sulphate, particularly when given too rapidly, may cause severe hypotension.

Risk factors for hypersensitivity (including anaphylactic reactions) to protamine sulphate:
- Allergy to fish
- Previous treatment with protamine insulin, protamine sulphate or protamine chloride
- Infertility in men
- Medical history of vasectomy (e.g. sterilisation)

Therefore if protamine sulphate is administered as a lifesaving measure to a patient with any of these conditions, the patient should be treated under closer surveillance.

Excessive dosage of protamine sulphate or when given in the absence of heparin or LMWH may induce prolonged coagulation time since protamine sulphate in itself has anticoagulant activity.

Rebound anticoagulant effect of heparin/LMWH with haemorrhage has been reported occasionally despite initial adequate heparin neutralisation by protamine sulphate.
This occurs more frequently in case of extra corporeal circulation in cardiovascular surgery, within 30 minutes to 18 hours after protamine sulphate administration. This rebound bleeding responds to further doses of protamine sulphate.

Rebound bleeding may also occur when protamine sulphate is used to reverse subcutaneous heparin or LMWH, reflecting continuous release of heparin or LMWH from the subcutaneous injection sites which act as depots.

Patients undergoing prolonged procedures involving repeated doses of protamine sulphate should be subject to careful monitoring of clotting parameters, e.g. activated clotting time (ACT), and as thrombocytopenia due to extracorporeal circulation may be aggravated by protamine sulphate, platelet count should be monitored.

With heparin overdose, in the absence of overt haemorrhage, serious consideration should be given as to whether protamine sulphate should be used and the risk/benefit ratio should be considered for the individual patient. The relatively short half life for heparin (especially if given intravenously) and the potential risk of administering protamine sulphate must be considered in the assessment.

This medicinal product contains less than 1 mmol (23 mg) sodium per 5 ml, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies other than studies with heparin and LMWH have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of protamine sulphate in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity.

Protamine sulphate is not recommended during pregnancy and in woman of childbearing potential not using contraception, unless the clinical condition of the woman strongly requires treatment with protamine sulphate.

Breast-feeding
It is unknown whether protamine sulphate is excreted in human milk. A risk to the infants cannot be excluded. Breast-feeding should be discontinued during treatment with protamine sulphate.

Fertility
There are no clinical or non-clinical studies with protamine sulphate regarding fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse reactions is not known as this cannot be estimated from the available data.

The most serious reported adverse reactions are hypotension, pulmonary hypertension and anaphylactic reactions.

Undesirable effects are listed by MedDRA SOC. Within each MedDRA SOC adverse reactions are presented in the order of decreasing seriousness.

Gastrointestinal disorders
Vomiting

Immune system disorders
Anaphylactic reaction (incl. anaphylactic shock, even fatal)
Hypersensitivity

Musculoskeletal and connective tissue disorders
Back pain

Respiratory, thoracic and mediastinal disorders
Pulmonary hypertension

Vascular disorders
Hypotension (incl. blood pressure decreased)*
Haemorrhage*Some of the reported hypotensive events may have anaphylactic background

Descriptions of selected adverse reactions
Hypersensitivity including immune-mediated allergic reactions (see section 4.4 for potential risk factors).

Symptoms like urticarial or other skin rashes, peripheral vasodilation, dyspnoea or angioedema have been observed and more severe reactions include bronchospasm, hypotension with cardiac and circulatory changes, loss of consciousness and cramps. Fatal anaphylactic shock has been seen after protamine administration.

Prolonged hypotension accompanied by bradycardia, cyanosis, stupor, syncope, loss of consciousness or transient cardiac asystole.

Too rapid administration may cause hypotension (transient or severe) or bradycardia and increase the risk for anaphylactic reaction.

Paediatric population
The observed safety profile is similar in children and adults.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

Clinical Effect of Overdose*:*
Overdose may cause haemorrhage, as protamine sulphate in itself has a weak anticoagulant effect. Furthermore, in volunteers with very high doses of protamine sulphate (800 mg/70 kg) typical signs of histamine release were observed in a dose-dependent way such as: itching, peripheral vasodilation, fatigue, malaise, nausea/vomiting, headache, hyperventilation and temperature elevation.

Treatment of Overdose*:*
In the event of haemorrhage due to protamine sulphate overdose, administration of the product should be discontinued. To determine that the protamine sulphate is contributing to the bleeding, the heparin titration test with protamine sulphate and the determination of plasma thrombin time are commonly used in this setting. For severe haemorrhage, transfusion of whole blood or fresh frozen plasma or other intervention may also be required. Hypotensive patients may require additional intravenous fluids, oxygen, adrenaline, dobutamine or dopamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes, ATC code: V03AB14.
Protamine sulphate is a strongly basic polycationic peptide, which is composed of a purified mixture of sulphates of peptides composed mainly of the basic amino acids arginine (more than 67%), proline, serine and valine. When

protamine sulphate combines with the strongly acidic heparin or low molecular weight heparin a stable complex is formed, lacking in anticoagulant activity.

Protamine sulphate neutralises the anticoagulant effect of heparin. It almost completely neutralises the antithrombin (anti IIa) activity of low molecular weight heparin (LMWH), and partially neutralises its anti Xa effect.

The degree of neutralisation of different LMWHs by protamine sulphate has been determined in-vitro. The results are summarised in the table below:

	Anti Xa neutralised	**Anti IIa Neutralised**
Reviparin	37%	>84%
Enoxaparin	46%	>87%
Nadroparine	51%	>89%
Dalteparin	59%	>93%
Tinzaparin	81%	>96%

Anti IIa activities were neutralised to below lower limit of quantification

5.2 Pharmacokinetic properties

Protamine sulphate has a rapid onset of action. Following intravenous administration, neutralisation of heparin occurs within 5-15 minutes.
The metabolic fate of the protamine-heparin/protamine-low molecular weight heparin complexes is unknown.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the safety evaluation which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Protamine sulphate solutions are incompatible with certain antibiotics, including several of the cephalosporins and penicillins.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

To be used immediately after opening of the ampoule.

When diluted for administration as a slow intravenous infusion the mixture should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml solution in colourless ampoules, (type I glass).
Pack sizes: 5 x 5 ml and 50 x 5 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

To be used immediately after opening of the ampoule.
Any remaining solution to be discarded.
May only be used if the solution is clear and the ampoule is intact.
Any unused product or waste material should be disposed of in accordance with local requirements.

Protamine sulphate LEO Pharma can be administered as a slow intravenous infusion in which case sodium chloride 9 mg/ml solution should be utilised.
Such mixtures should not be stored.

7 MARKETING AUTHORISATION HOLDER

LEO Pharmaceutical Products
Industriparken 55
2750 Ballerup
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 1025/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th November 2006

Date of last renewal: 4th August 2010

10 DATE OF REVISION OF THE TEXT

October 2014