**Package leaflet: Information for the patient**
**Protamine sulphate LEO Pharma 1400 anti-heparin IU/ml**
**(corresponds to 10 mg/ml)**
**solution for injection and infusion**

Protamine sulphate

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you**.
- Keep this leaflet. You may need to read it again.
- A doctor or nurse usually administers this product. If you have any further questions ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Protamine sulphate LEO Pharma is and what it is used for

The active ingredient is protamine sulphate, which is used as an anti-heparin, to block the action of heparin and low molecular weight heparins, and to reduce the effect of these substances on the body.

Heparins are used to prevent your blood from clotting and they may cause bleeding.

You may be given this medicine:

- To help stop bleeding which has been caused by heparin/low molecular weight heparin
- To prevent a lot of bleeding if you have been treated with heparin/low molecular weight heparin and are going to have surgery
- To reverse the effect of heparin used for some types of heart surgery

## 2. What you need to know before you use Protamine sulphate LEO Pharma

**Do not use Protamine sulphate LEO Pharma:**
if you are allergic to protamine sulphate or any of the other ingredients of this medicine (listed in section 6)

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before using Protamine sulphate LEO Pharma

- if you are a diabetic using insulin (particularly protamine insulin)
- if you are allergic to fish
- if you are an infertile man (unable to have children) or if you have had a vasectomy (an operation that makes a man sterile)
- if you have previously been treated with protamine sulphate, protamine insulin or protamine chloride

If you already have been given your injection, please tell the hospital staff if any of the above applies to you. If you are unsure, please talk to your own doctor.

**Children and adolescents**
Protamine sulphate LEO Pharma is not indicated for use in children and adolescents.

**Other medicines and Protamine sulphate LEO Pharma**
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

**Pregnancy and breast-feeding**
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, nurse or pharmacist for advice before taking this medicine.
There is no information available regarding the use of this product in pregnant women.
Protamine sulphate LEO Pharma should not be used unless clearly necessary.

Breast-feeding
If you are breast-feeding, ask your doctor, nurse or pharmacist for advice before taking this medicine.
There is no information available regarding the use of this product in breast-feeding women.
If treatment with Protamine sulphate LEO Pharma is necessary, breast-feeding should be interrupted.

**Driving and using machines**
Protamine sulphate LEO Pharma has no or negligible influence on the ability to drive and use machines.

**Protamine sulphate LEO Pharma contains sodium**
This medicine contains less than 1 mmol (23 mg) sodium per 5 ml, i.e. essentially “sodium-free”.

## 3. How to use Protamine sulphate LEO Pharma

Your doctor will decide how much Protamine sulphate LEO Pharma is right for you. This depends on the results of blood tests to find out how much heparin has to be blocked.

Protamine sulphate LEO Pharma is intended for intravenous use, and may be given by a slow injection (over about 10 minutes) into a vein or it may be added to your “drip” solution.
You may need additional doses, especially if a low molecular weight heparin needs to be reversed or if your surgery takes a long time.
You will not be given more than 5 ml of this medicine in any 10-minute period.

**If you have been given more Protamine sulphate LEO Pharma than you should**
This may interfere with the blood clotting process by increasing the time taken for blood to clot.

If you have any further questions on the use of this product, ask your doctor, nurse or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects:**
If you experience any of the following, you should immediately contact your doctor, nurse or local hospital for emergency help:
- **Severe allergic reaction**. Symptoms include severe breathing problems, wheezing, swelling of face and lips, heart problems, collapse (fainting due to low blood pressure)
- **High blood pressure in the lungs.** Symptoms include severe breathing problems
- **Severe and longer lasting low blood pressure**. Symptoms include a slow heart rate, blue skin, feeling faint or collapsing (especially if Protamine sulphate LEO Pharma was administered to quickly)

**The following less serious side effects have been observed with the administration of Protamine sulphate LEO Pharma**:
- Low blood pressure. Symptoms include dizziness
- Vomiting
- Back pain
- Bleeding
- Allergic reaction, similar to a nettle rash or other skin rashes. Symptoms include feeling warmth, flushing of the skin, breathlessness and swelling of the deeper layers of the skin (occasionally with swelling of the tongue and airway).

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.
[To be completed nationally]

## 5. How to store Protamine sulphate LEO Pharma

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.
- 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.
- When diluted for administration as a slow intravenous infusion the mixture should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Protamine sulphate LEO Pharma contains**
- The active substance is protamine sulphate. 1 ml contains 1400 anti-heparin IU protamine sulphate (corresponds to 10 mg), 5 ml contain 7000 anti-heparin IU protamine sulphate (corresponds to 50 mg).
- The other ingredients are: sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections

**What Protamine sulphate LEO Pharma looks like and contents of the pack**
This product is provided as a solution for injection, and infusion which is a clear, colourless liquid.
Ampoules of 5 ml. Pack size of 5 or 50 ampoules.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
LEO Pharma A/S
55 Industriparken, DK-2750 Ballerup, Denmark

**Manufacturer**
CENEXI SAS

52, rue Marcel et Jacques Gaucher, 94120 Fontenay-sous-Bois, France

**This leaflet was last revised in: 2014-09-08**

Detailed information on this medicine is available on the web site of:
{name of MS/Agency}

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**Please cut along this line and retain this part of the leaflet. Give the remaining part of the leaflet to the patient.**

**The following information is intended for healthcare professionals only**

**Protamine sulphate LEO Pharma**
**1400 anti-heparin IU/ml**
**(corresponds to 10 mg/ml)**
**solution for injection and infusion**

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

**See full Summary of Product Characteristics (SmPC) for further details.**

**Therapeutic Indications:** Protamine sulphate can be used to counteract the anticoagulant effects of heparin or LMWH (See SmPC).

**Posology and Method of Administration**
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). Ideally, the dose should be guided by blood coagulation studies. The activated partial tromboplastin time (APTT), activated clotting time (ACT), anti Xa and bedside protamine neutralization 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.

***Neutralization of Heparin***
1 ml of Protamine sulphate LEO Pharma (10 mg protamine sulphate) will neutralize 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.

***Neutralization 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 neutralizes the various LMWHs to a different extent; therefore, for each LMWH the manufacturer's own guidelines should be consulted in case of an overdose. 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 neutralization 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.

**Special precautions for disposal**
To be used immediately after opening of the ampoule.
Any remaining solution to be discarded.
May only be used if the solution is clear, without visible particles 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 should be utilised. Such mixtures should not be stored.