LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Protaminsulfat LEO Pharma 1400 anti-heparin IE/ml
(Protamine sulphate, salmon)

SE/H/562/01/MR

This module reflects the scientific discussion for the approval of Protaminsulfat LEO Pharma. The procedure was finalised at 2006-08-04. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

LEO Pharma has applied for a marketing authorisation for Protaminsulfat LEO Pharma 1400 anti-heparin IE/ml, solution for injection and infusion. The active substance is protamine sulphate extracted from salmon milt.

The product is indicated for use as an antidote for heparin and low-molecular-mass heparin. Protamine sulphate neutralises the anticoagulant effect of heparin and the anti-IIa activity of LMMH (low molecular weight heparin) and partially the anti-Xa activity of LMMH.

During the procedure, a list of potential serious risk to public health concerns were raised by one CMS and a CMD referral was initiated. Following the discussion in CMD it was agreed that it is most suitable to express the strength of the drug product in anti-heparin IU/ml. The assay in the Ph Eur monograph determines the number of IUs of heparin sodium BRP that is neutralised per mg of the drug substance and the amount of drug substance loaded during manufacturing is based on activity and not protein amount.

It was pointed out by some member states that the now proposed potency labelling may lead to confusion with regard to dosing in relation to the labelling of other already approved protamine sulphate products (labelled in mg/ml). This is however taken care of since the strength is declared in both anti-heparin IU/ml and mg/ml in section 2 of the SPC as well as in the labelling. The CMD referral was ended positively and approval could be granted by all concerned member states.

II. QUALITY ASPECTS

II.1 Introduction

Protaminsulfat LEO Pharma is presented in the form of a solution for injection and infusion containing 1400 anti-heparin IU/ml of protamine sulphate which corresponds to approximately 10 mg/ml. The excipients are sodium chloride, hydrochloric acid, sodium hydroxide and water for injections. The solution is filled in ampoules of colourless glass.

II.2 Drug Substance

The drug substance complies with the requirements in the Ph Eur monograph for Protamine Sulphate. Information on protamine sulphate was supplied in the form of an ASMF but during the MR procedure transferred to 3.2.S.

Protamine sulphate is a white or off-white, hygroscopic powder which is sparingly soluble in water and practically insoluble in alcohol. All protamines are mixtures of several similar proteins with minor sequence differences. The chum salmon protamine sulphate has four major species with different amino acid sequences. The average molecular mass is between 5,000 and 5,500. The degree of detail in the characterisation of protamine sulphate is considered satisfactory. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and limits and the analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the shelf life.

II.3 Medicinal Product

Protaminsulfat LEO Pharma 1400 anti-heparin IE/ml, solution for injection and infusion is formulated using excipients described in the current Ph Eur.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

The drug substance protamine sulphate is extracted from the sperm of the Salmonid species, *Oncorhynchus keta*. As this is a biological product for medical use a virus risk assessment was prepared on the risk of transfer of zoonotic organisms from fish to humans. The risk assessment, made by an external expert, concludes that there is no reason to regard virus infections in *Oncorhynchus keta* as zoonosis, and there is no evidence of risk of transfer to man of virus from this salmon species. The conclusion of the risk assessment is found acceptable.

Compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been declared by the company. No material used in the manufacturing originates from animal species susceptible to TSE.

III. NON-CLINICAL ASPECTS

III.1 Toxicology

This application was based on published references. An environmental risk assessment has been carried out. Regarding animal efficacy, protamine was shown to neutralise the hard endpoint of clinical bleeding induced by a LMWH preparation, as well as the haemorrhagic prolongation induced by heparin.
Protamine sulphate is a medicinal substance with well-established use. Accordingly, for this type of product particular attention should be paid to the preclinical areas reproduction toxicity, genotoxicity and carcinogenicity as outlined by CPMP/SWP (CPMP/SWP/799/95/draft: released for consultation). A risk assessment should also be done taken into account the impurity profile. The lack of reproduction toxicity studies is considered acceptable in light of the indication and the proposed warning in SPC 4.6. The presented published data showed that the tested protamine sulphate preparation was devoid of mutagenic potential in bacteria and clastogenic potential in vitro in mammalian cell. Data on oncogenic potential is not necessary. It was considered that there is no apparent toxicity concern about the impurity profile of Protamine sulphate LEO Pharma. There were thus no outstanding issues and Protamine sulphate LEO Pharma was approved from a preclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No formal pharmacokinetic studies have been performed in man, and conclusions on the distribution and elimination of protamine sulphate must be based on the few animal studies. The dosing recommendations given by the Applicant are primarily supported by well-established clinical routines for neutralisation of heparin but some additional support is provided from the preclinical studies, in vitro studies and the pharmacodynamic studies in humans. Dosing recommendations in reversal of the effects of LMWH are primarily supported by the experimental in vitro and in vivo studies. There is only sparse documentation on the distribution, metabolism and elimination of protamine sulphate but it can be concluded that the half-life of protamine sulphate in the species investigated is short (appr. 20 minutes in rats) and, as can be judged from the effects on coagulation, it seems to be of the same magnitude in humans.

IV.2 Pharmacodynamics

The mechanism through which protamine antagonises heparin and LMWHs has not been completely elucidated but it most probably occurs through an acid-base interaction. Heparin is a negatively charged, sulphated, glycosaminoglycan, which is strongly acidic and induces anticoagulation by activating the effects of antithrombin III to inactivate factors Xa and IIa (thrombin). Protamine is strongly basic and when combined with heparin a stable complex is formed which has no anticoagulant activity.
There is general agreement, based on animal experiments and clinical experience, that protamine sulphate neutralises not only the anticoagulant effects of unfractionated heparin but also the anti-haemostatic effects.
It was reported quite early in the development of LMWHs that although APTT values are easily normalised after administration, that anti Xa activity was only partially neutralized in vitro. The results of the in vitro studies performed on human plasma are essentially similar and seem to confirm that it is possible to neutralise the ant-IIa activity of LMWHs completely or almost completely with protamine sulphate. The Applicant has performed an in vitro study demonstrating the capacity of protamine sulphate to neutralise the different anticoagulant effects of different LMWHs. The results are supported by the available human in vivo studies in healthy volunteers. The anti-Xa effect is neutralised to a varying degree, which possibly is related to the mean molecular weight and/or sulphate content of the LMWH.

IV.3 Clinical efficacy

No formal clinical pharmacological studies of the reversal of the anticoagulant effects of heparin by protamine sulphate in patients have been performed by the sponsor and much of the data is from published literature. The capacity of protamine sulphate to neutralize heparin and the associated bleeding tendency has been demonstrated in large clinical observational studies in cardiopulmonary bypass surgery. The use of protamine for neutralisation of heparin in connection with surgery and in cases of overdoses and/or bleedings can be considered as well-established.
The limited documentation from human in-vivo studies on the capacity of protamine sulphate to neutralise the anticoagulant activity of LMW heparins seems to essentially confirm the in vitro findings that the global clotting test, such as APTT, are completely or almost completely neutralised. The anti-Xa activity, however, is only partially neutralised and to an extent somewhat varying between different LMWHs. That a haemostatic effect also is achieved is less well documented for LMWHs than for heparin, but has support from animal experiments.

Furthermore, that the anti-haemostatic properties of LMWHs are related to the anticoagulant effects can be regarded as generally accepted.

IV.4 Clinical safety

There have been no reports of adverse events from clinical trials performed by the Applicant. However in a phase 1 study, one subject who had been given 129.5 mg of Protamine Sulphate experienced an allergic reaction, including a drop in blood pressure and palpitations.
It is estimated that approximately 6.5 million patients have been exposed to protamine sulphate in the last 12 years.
In total 19 case reports representing 28 adverse events have been reported spontaneously to the Company. Seven of these 15 reports were received via the WHO notification system. Of the 28 adverse events, 14 were considered serious. Of the 28 adverse events, 22 recovered without sequelae, 2 had not resolved and in 1 case the outcome was unknown. The remaining 3 adverse events occurred in a patient who died from anaphylactic shock/cardiac failure.
The 28 adverse events are as listed:

Backpain	5
Anaphylactoid reaction/shock	4
Hypotension	4
Nausea/Vomiting	3
Circulatory failure	2
Haemorrhage	1
Headache	1
Increased Sweating	1
Dizziness	1
Cardiac Arrest	1
Death	1
Bradycardia	1
Urticaria	1
Convulsions	1
Respiratory Insufficiency	1

Allergic or anaphylactic reactions to protamine sulphate seems to be the most common and serious adverse effect of protamine sulphate and is thought to be partly due to residual fish antigens that remain after purification and occurs in allergic individuals. Such reactions are reported to rarely result in severe cardiovascular collapse, bronchospasm and even death. Even in subjects who are not allergic, rapid intravenous administration has caused hypotension, bradycardia, transient flushing and a feeling of warmth. These adverse effects are minimized when the injection is given slowly (slow IV push over 10 minutes).
Allergic reactions to protamine sulphate have been reported to be more common in men who have previously had a vasectomy. The mechanism is postulated to be that antibodies against nucleoprotamines.
No information is available with regards to the use of protamine sulphate in neonates or children.
As the metabolism and excretion pathways for protamine sulphate are unknown, it is unknown whether renal or hepatic disease influences the safety of protamine sulphate.
With regards to pregnancy there are only reports on the administration of the protamine sulphate around the time of delivery. Wether protamine sulphate has safety concerns in earlier stages of pregnancy, especially with regards to teratogenicity, is unknown

IV.5 Discussion on the clinical aspects

The capacity of protamine sulphate to neutralize heparin has been well elucidated in experimental work and in large clinical observational studies, especially in cardiopulmonary bypass surgery. It can be regarded as generally accepted that the anticoagulant effects as well as the anti-haemostatic effects of heparin can be reversed by protamine sulphate to a clinically relevant extent and its use for this purpose can be considered as well-established.
The primary pharmacodynamic effects of protamine sulphate on the anticoagulant effects of LMWHs have been rather well characterised in in vitro experiments. The study performed by the Applicant provides additional information and the results seem to be in line with the results published by other investigators. To what extent protamine sulphate restores haemostatic function in an increased bleeding tendency induced by LMWH remains somewhat uncertain. There is, however, from animal experiments and from the known pharmacodynamic effects, reason to conclude that protamine sulphate is able to at least partially reverse the bleeding tendency. It can be regarded as generally accepted that there is a relationship between the anticoagulant effects (anti-Xa and anti-IIa activity) and bleeding tendency. Normal doses of LMWH often only cause small prolongations of global clotting tests (such as APTT). However, in patients given high doses of LMWH the global clotting tests can be considerably prolonged and it has been sufficiently demonstrated that these effects can be completely or almost completely reversed. That protamine sulphate has the capacity to at least partially reverse the anti-haemostatic effects of LMWH is also reflected in the current SPCs (section 4.9) for several LMWHs.
The safety profile of protamine sulphate is rather well characterised after over 50 years of clinical use. The major safety issue is the risk for severe anaphylactic reactions where groups of patients at increased risk can be identified. This is reflected in the approved SPC.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The applicant has made a commitment to perform user testing and submit the results within 3 months from the end of the procedure.

The risk/benefit ratio is considered positive and Protaminsulfat LEO Pharma 1400 anti-heparin IE/ml, solution for injection and infusion is recommended for approval.

In connection with the MRP approval the applicant prepared a list of post-approval commitments and before the end of 2006 the applicant will submit an updated Module 3.2.S and a type II variation to include an additional identity test for the drug substance.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se