Prosulf 10mg/ml solution for injection
(protamine sulphate)
PL 29831/0520

UKPAR

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Prosulf 10mg/ml solution for injection

(protamine sulphate)

PL 29831/0520

LAY SUMMARY

The MHRA granted Wockhardt UK Limited a Marketing Authorisation for the medicinal product Prosulf 10mg/ml solution for injection on 8th March 2013. This medicine is subject to restricted medical prescription and is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

Prosulf 10mg/ml solution for injection contains, as its active, 10mg/ml of protamine sulphate.

This application was submitted as an abridged simple national application under Article 10(c) according to Directive 2001/83/EC, as amended; an informed consent application.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Prosulf 10mg/ml solution for injection outweigh the risks, hence a Marketing Authorisation has been granted.
ProSulf 10mg/ml solution for injection

(protamine sulphate)

PL 29831/0520

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to Wockhardt UK Limited for the medicinal product Prosulf 10mg/ml solution for injection on 8th March 2013. This product is a restricted prescription only medicine.

This application was submitted as a stand-alone abridged simple national application under Article 10(c) according to Directive 2001/83/EC, as amended; an informed consent application.

Prosulf 10mg/ml solution for injection is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

Prosulf 10mg/ml solution for injection contains, as its active, 10mg/ml of protamine sulphate. Prosulf 10mg/ml solution for injection is a clear, colourless solution supplied in 5ml and 10ml neutral type I hydrolytic glass ampoules in pack sizes of 10 ampoules in cartons.

The application makes reference to the marketing authorisation for Prosulf injection 1% (PL 29831/0180) which was granted on 27th June 2007 via a change of ownership from PL 04543/0234, MAH CP Pharmaceuticals Ltd. This ‘informed consent’ application was granted on 8th March 2013.
QUALITY ASSESSMENT

I REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORIZATION

Suitable manufacturing authorisations (MAs) have been provided for each of the listed sites.

II INTRODUCTION

This application makes reference to the marketing authorisation for Prosulf® 10mg/ml Solution for Injection, PL 29831/0180. This product was authorised in the UK in June 2007 by means of a change of ownership procedure from PL 04543/0234, Marketing Authorisation Holder (MAH) CP Pharmaceuticals Ltd to PL 29831/0520. Wockhardt UK Ltd is the current MAH.

A suitable letter of access has been provided by Wockhardt UK Ltd (letter dated 10 February 2011) to use their dossier and that they are in possession of all the necessary data to support this application including the quality dossier.

Information has been provided to confirm the suitability of the Quality Expert. A QOS Module 2 has been provided specifically for this application.

The applicant has provided adequate justification for the absence of an environmental risk assessment.

Legal basis
This is an ‘informed consent’ application submitted under Article 10c Directive 2001/83/EC as amended and using the BROMI checklist for Protamine Sulphate solution for injection. The MAH is Wockhardt UK Ltd, and evidence of establishment of the MAH in the EEA (UK national) was provided.

Use
Prosulf 10mg/ml solution for injection is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

Scientific advice
N/A

Legal status
POM

III DRUG SUBSTANCE

III.1 MANUFACTURE

Starting Material
The supplier of the raw material and active substance is identical to that of the reference MA.
Active Substance
The validation of the processing and purification of the salmon milt at active substance manufacturing site performed in 2000 was used to determine and verify the suitability of the current standard procedures and controls. It was considered adequate to meet the requirements for the starting material and drug substance (DS) as evaluated in the original MA.

Viral safety is claimed as assured by the heating process involved in production. No viral safety issues are outstanding for the reference PL.

The active substance manufacturer details have been provided.

III.2 CONTROL OF DRUG SUBSTANCE

The drug substance specification (DSS) is identical to that currently approved for the reference PL.

Justification of Specifications
The finished product specification (FPS) refers directly to the current relevant Ph.Eur. monograph for protamine sulphate.

IV. DRUG PRODUCT

IV.1 MANUFACTURE

Finished Product
The formulation of the finished product is identical to the of the reference product licence (PL).

The reference product MA comprises a 5ml ampoule presented in a carton containing 10 ampoules. This is identical to the proposed pack size for the BROMI application.

The applicant intends to use an identical Ph.Eur. compliant glass ampoule as the immediate container/closure as the reference PL.

Shelf-life is identical to the reference product (48 months).

Storage conditions are identical to the reference product (do not store above 25°C).

The proposed finished product manufacturers, quality control (QC) sites and assembler and packagers are identical to that approved in the reference PL.

Suitable manufacturing authorisations have been provided for each of the listed sites.

A flow chart was provided showing the different sites involved in the manufacturing process.

The method of manufacture corresponds to that on file for the reference product.

IV.2 CONTROL OF DRUG PRODUCT

Specification
The specification for finished product is identical to that currently approved for the reference PL.

**Justification of Specifications.**
The FPS refers directly to the current relevant Ph.Eur. monograph for protamine sulphate.

**Reference Standard**
An in-house reference material has been prepared and qualified by the applicant in accordance with the procedures approved for PL 29831/0180.
The following reference standard (identical to PL 29831/180) is proposed for this product.

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<th>Test Performed</th>
<th>Reference Standards/Materials</th>
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<tr>
<td>Protamine sulphate assay</td>
<td>Heparin sodium EPBRP (100%) (PhEur) (Stock ID: 1929949)</td>
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</table>

**V. CONTROL OF OTHER STARTING MATERIALS & TSE ISSUES**
In-line with the MAA form and reference information held on Sentinel, all the respective excipients are expected to meet the same Ph.Eur. requirements as the reference PL.

A suitable statement has been provided by the applicant, for each respective excipient manufacturer.

Material of animal or human origin has been qualified, and where appropriate, where appropriate declarations of their suitability for use in pharmaceuticals with respect to TSE/BSE risk have been addressed.

**Regional Information**
Process Validation Protocols for the Drug Product were provided and are satisfactory.

A declaration was provided, relating to the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products, for the drug substances.
A declaration was provided, relating to the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products, for the finished product.

The applicant has provided confirmation of the GMP status for the manufacturer of the active product and for all manufacturers of the finished product which are satisfactory.

**VI. SPC**
No issues have been identified with respect to the quality sections of the SPC.

**VII. Patient Information Leaflet**
This is acceptable.

*(Assessment of User Testing has been addressed in the Clinical AR)*
VIII. Label
This is acceptable.

IX. Assessor’s Overall Conclusions
Marketing Authorisation may be granted.
I INTRODUCTION

I.1 TYPE OF APPLICATION AND ASPECTS ON DEVELOPMENT
This is a National application, submitted under Directive 2001/83/EC, as amended, Article 10(c) “informed consent” application for marketing authorisation. This application is for Protamine sulphate 10 mg/ml solution for injection (ATC code V03AB14).

Protamine sulphate 10 mg/ml solution for injection, PL 29831/0180, was authorised in the UK on 27 June 2007: this licence was obtained by a change of ownership procedure: the previous licence, PL 04543/0234, had been owned by CP Pharmaceuticals Ltd and was granted in 1991. The current licence PL 29831/0180 is held by Wockhardt UK Ltd.

Prosulf 10 mg/ml Solution for Injection and Protamine Sulphate 10mg/ml Solution for Injection is indicated for the following indication (taken from proposed SmPC):

Protamine sulphate is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

No new non-clinical studies have been conducted in support of this application, a summary of the pharmacology, pharmacokinetics and toxicology has been provided in the Non-Clinical Overview, with reference to literature.

I.2 GLP ASPECTS
For the published data it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted would have been in compliance with the standards prevailing at the time.

II PHARMACOLOGY

Protamine sulphate is a mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. It is sparingly soluble in water and practically insoluble in alcohol. It is the subject of monographs in Ph.Eur.7.0 and USP 33 and pharmacopoeal forms are described (see BP2010).

The mechanism of action is not fully understood although Protamine is a highly effective antidote to heparin. Protamine is a strongly basic protein that combines with strongly acidic heparin to form a stable inactive complex. This neutralises the anticoagulant action of heparin and is effective in the treatment of haemorrhage resulting from severe heparin or low-molecular weight heparin overdosage. Protamine is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is usually given as the sulphate, although the hydrochloride may also be used.

Protamine has a weak anticoagulant effect of its own and it is also used as an excipient for some injectable insulin formulations in which it apparently prolongs the euglycaemic phase. It has also been used a food preservative.

There is evidence from animal studies that Protamine, when administered long-term by mouth, has a favourable effect upon serum lipid concentrations. The mechanism is likely
to cause increases in the activities of the carnitine palmitoyltransferase-2 and acyl-CoA oxidase enzymes. This is assumed to be the effect in humans, though this has not been confirmed. Protamine has also been shown to reduce intestinal fat absorption and to have antibacterial effects.

The effect of protamine sulphate on factor Xa (FXa) and the factor Xa-antithrombin complex has been studied. Human factor Xa and human antithrombin (AT) form primary, secondary and tertiary complexes. The addition of protamine sulphate stimulates a transformation from free FXa to FXaβ and degradation to inactive FXaγ, as well as transformation of FXaα-AT complexes to FXaβ-AT complexes. Additionally, it promotes digestive degradation from 1" to 3" complexes and FXaγ by the active enzyme. It further promotes reduction in total complex formulation as a function of stimulation of hydrolysis of FXa moieties. These effects are proportional to protamine concentration. Historical data from clinical use of protamine sulphate in man provide the most useful evidence of the pharmacology of this preparation.

II.1 ASSESSOR’S OVERALL CONCLUSIONS ON PHARMACOLOGY

No new pre-clinical data have been submitted for this application, as pre-clinical data is superseded by clinical experience. The applicant’s summary is acceptable.

III PHARMACOKINETICS

There is only limited data on the pharmacokinetics for protium sulphate, as only one study in man could be found. Healthy adults were intravenously dosed with protium sulphate and the kinetics examined.

Absorption

In normal individuals during the initial infusion, the AUC is concave, which conflicts with the assumptions of conventional compartmental linear pharmacokinetics, in which a convex curve is predicted. The onset of action has been reported to occur 30 - 60 seconds after intravenous dosing.

In healthy humans, protamine concentrations were less than the limit of detection after 20 min or less. Protamine concentration-versus-time data were significantly different between men and women. Specifically, weight-adjusted protamine dosing resulted in significantly decreased AUC and significantly greater plasma clearance (CL) and volume distribution at steady state (Vss) in women than in men.

Metabolism and Excretion

The mechanisms are not known although presumably peptidases play a part. It is also possible that the elimination of protamine/heparin complexes could be faster or slower than elimination of free protamine, and further studies will be necessary to determine whether these theoretical differences are present.

III.1 ASSESSOR’S OVERALL CONCLUSIONS ON PHARMACOKINETICS

No new pre-clinical pharmacokinetic data have been submitted for this application, as pre-clinical data is superseded by clinical experience. The applicant’s summary is acceptable.
IV TOXICOLOGY
The animal toxicology of Protamine Sulphate as reported in the literature is relatively sparse. In common with most drugs in clinical use for more than 2 decades, relevant information relating to the toxicology of Protamine Sulphate in man has accumulated, providing insight into its risks that makes further animal experiments largely redundant. In the non-clinical overview, the aspects of toxicology such as possible carcinogenicity, mutagenicity, effects upon pregnancy, effects on the newborn, on children, elderly individuals and a few other groups at risk have revealed there to be no animal toxicology cited in the literature to indicate that any of these risk factors might be present for protamine sulphate.

IV.1 ECOTOXICITY/ENVIRONMENTAL RISK ASSESSMENT
No formal Environmental Risk Assessment has been provided. According to the guideline on the environmental risk assessment of medicinal products for human use, an environmental risk assessment (ERA) is required for all new marketing authorisation applications for a medicinal product. The applicant has argued that as Protamine Sulphate 10mg/ml Solution for Injection is a generic product it would only replace the use of the currently marketed product rather than add to its use, and hence the exposure of the environment to Protamine Sulphate 10 mg/ml Solution for Injection (PL29831/0520) is not likely to be increased. This justification is acceptable.

IV.2 ASSESSOR’S OVERALL CONCLUSIONS ON TOXICOLOGY
No new toxicity tests were performed and review of literature revealed sparse findings of animal toxicology. In any effect clinical experience would supersede the findings of pre-clinical findings. No concerns are raised in respect to impurities. A proper justification for not performing an environmental risk assessment in accordance with the EU guideline (CHMP/SWP/4447/00) has been provided.

V ASSESSOR’S OVERALL CONCLUSIONS
Published literature and non-clinical data have been reviewed by Dr W. P. Leary, an independent consultant clinical pharmacologist. The Expert has adequate experience of pharmacology and toxicology. The Non-Clinical Overview refers to 13 publications up to 2011. The review is acceptable and the pharmaco-toxicological properties of protamine sulphate have been well defined and extensive clinical experience has been gained.

There are no objections to the approval of Protamine Sulphate 10 mg/ml Solution for Injection from a non-clinical point of view.
1 Introduction

1.1 Type of Application and Regulatory Background

This national application was made in the United Kingdom under EU Directive 2001/83/EC as amended, Article 10(c) “informed consent” application for marketing authorisation for Protamine sulphate 10mg/mL for injection, as listed above.

Protamine sulphate 10mg/mL for injection, PL 29831/0180, was authorised in the UK in June 2007: this licence was obtained by a change of ownership procedure: the previous licence, PL 04543/0234, had been owned by CP Pharmaceuticals Ltd. The current licence PL 29831/0180 is held by Wockhardt UK Ltd.

1.2 Clinical Background

Protamine is used as an antidote in heparin overdose: protamine is a basic protein that is administered intravenously and that binds to acidic heparin to form a stable, inactive complex thereby neutralising the anticoagulant action of heparin. Protamine may be used before or during surgery to neutralise the effect of heparin.

1.3 Indications: the following indications are taken from the submitted SPC:

4.1 Therapeutic indications

Protamine sulphate is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

1.4 Posology and method of administration: the following posology and method of administration are taken from the submitted SPC:

4.2 Posology and method of administration

Adults:

Prosulf should be administered by slow intravenous injection over a period of about 10 minutes. No more than 50mg of protamine sulphate should be given in any one dose.

The dose is dependent on the amount and type of heparin to be neutralised, its route of administration and the time elapsed since it was last given, since heparin is continuously being excreted. Ideally, the dose required to neutralise the action of heparin should be guided by blood coagulation studies or calculated from a protamine neutralisation test.

In gross excess, protamine itself acts as an anticoagulant.

Neutralisation of unfractionated (UF) heparins:

1mg of protamine sulphate will usually neutralise at least 100 international units of mucus heparin or 80 units of lung heparin. The dose of protamine sulphate should
be reduced if more than 15 minutes have elapsed since intravenous injection.

For example, if 30-60 minutes have elapsed since heparin was injected intravenously, 0.5-0.75mg protamine sulphate per 100 units of mucous heparin is recommended. If two hours or more have elapsed, 0.25-0.375mg per 100 units of mucous heparin should be administered.

If the patient is receiving an intravenous infusion of heparin, the infusion should be stopped and 25-50mg of protamine sulphate given by slow intravenous injection.

If heparin was administered subcutaneously, 1mg protamine sulphate should be given per 100 units of mucous heparin - 25-50mg by slow intravenous injection and the balance by intravenous infusion over 8-16 hours.

In the reversal of UF heparin following cardiopulmonary bypass, either a standard dose of protamine may be given, as above, or the dose may be titrated according to the activated clotting time.

Patients should be carefully monitored using either the activated partial thromboplastin time or the activated clotting time, carried out 5-15 minutes after protamine sulphate administration. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin.

Neutralisation of low molecular weight (LMW) heparins:

A dose of 1mg per 100 units is usually recommended but the manufacturer's own guidelines should be consulted.

The anti-Xa activity of LMW heparins may not be completely reversible with protamine sulphate and may persist for up to 24 hours after administration.

The longer half-life of LMW heparins (approximately twice that of UF heparin) 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 heparin dose.

Theoretically, the dose of protamine sulphate should be halved when one half-life has elapsed since the last LMW heparin dose. Intermittent injections or continuous infusion of protamine sulphate have been recommended for the neutralisation of LMW heparin following subcutaneous administration, as there may be continuing absorption from the subcutaneous depot.

Patients should be carefully monitored. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin, especially low molecular weight heparin.

Elderly:

There is no current evidence for alteration of the recommended dose.

Children:

Safety and efficacy in children have not been established. Not recommended.
2. General comments

GCP Aspects: n/a (the current product is for intravenous administration, a bioequivalence study is not required)

Orphan Medicinal Product: n/a

Paediatric Development Programme: n/a

Scientific Advice: not sought by applicant.

Pharmacovigilance System
It is considered that the Pharmacovigilance system as described by the applicant is satisfactory.

Risk Management Plan: n/a for a generic medicinal product

Periodic Safety Update Report
The applicant has aligned the current product PSUR cycle to that of Wockhardt UK Prosulf 10 mg/ml solution for injection licence (PL 29831/0180). The proposed data-lock point for the next PSUR for Prosulf 10 mg/ml solution for injection licence is 30th April 2013. The PSUR and renewal application will be submitted within 60 days of the data-lock point i.e. by 30th June 2013.

3. Clinical aspects

Clinical Pharmacology: Pharmacokinetics & Pharmacodynamics
Pharmacokinetics and pharmacodynamics have been previously assessed for PL 29831/0180 and found to be acceptable: there would not be any particular concerns regarding the current product.

Clinical Efficacy & Safety
Clinical safety and efficacy have been previously assessed for PL 29831/0180 and found to be acceptable: there would not be any particular concerns regarding the current product.

Clinical Expert Report
The Clinical Expert report is signed and dated 6th March 2011 by an appropriately qualified Physician with extensive clinical experience including post-graduate experience in Clinical Pharmacology.

Assessor comment: the Clinical Expert Report is acceptable.

The Clinical Overview summarises the clinical pharmacology, clinical safety & efficacy and benefit-risk of protamine. The Overview refers to 12 publications up to 2011.
Assessor comment: the Clinical Overview is acceptable.

4. **Product Literature**

SPC: the applicant has copied the SPC for PL 29831/0180

Patient Information Leaflet: the applicant has copied the PIL for PL 29831/0180

PIL user test: the applicant has submitted the user test for PL 29831/0180: this user test was accepted in June 2008:

Assessor comment: the SPC, PIL and PIL user-test are considered to be acceptable from the clinical perspective

5. **Overall Conclusions**

The overall benefit-risk balance is considered to be positive from the clinical perspective.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Prosulf 10mg/ml solution for injection are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Based on a review of the literature, the established efficacy and safety of Prosulf 10mg/ml solution for injection was satisfactorily and critically summarised.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety data were submitted. Extensive clinical experience with Prosulf 10mg/ml solution for injection is considered to have demonstrated the therapeutic value of the product. The risk: benefit is, therefore, considered to be positive.
Prosulf 10mg/ml solution for injection

(protamine sulphate)

PL 29831/0520

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application 6th June 2011
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 27th June 2011
3. Following assessment of the submitted data, the MHRA sent a request for further information (RFI) to the MAH on 19th September 2011
4. The MHRA received a response from the MAH on 11th October 2011
5. Following assessment of the submitted data, the MHRA sent a RFI to the MAH on 12th October 2011
6. The MHRA received a response from the MAH on 20th October 2011
7. Following assessment of the submitted data, the MHRA sent a RFI to the MAH on 20th October 2011
8. The MHRA received a response from the MAH on 14th November 2011
9. Following assessment of the responses the MHRA granted the application on 8th March 2013
Prosluf 10mg/ml solution for injection

(protamine sulphate)

PL 29831/0520

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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Prosulf 10mg/ml solution for injection

(protamine sulphate)

PL 29831/0520

SUMMARY OF PRODUCT CHARACTERISTICS
1 NAME OF THE MEDICINAL PRODUCT
Prosulf 10mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Protamine Sulphate 10mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Protamine sulphate is used to counteract the anticoagulant effect of heparin: before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

4.2 Posology and method of administration
Adults:

Prosulf should be administered by slow intravenous injection over a period of about 10 minutes. No more than 50mg of protamine sulphate should be given in any one dose.

The dose is dependent on the amount and type of heparin to be neutralised, its route of administration and the time elapsed since it was last given, since heparin is continuously being excreted. Ideally, the dose required to neutralise the action of heparin should be guided by blood coagulation studies or calculated from a protamine neutralisation test.

In gross excess, protamine itself acts as an anticoagulant.

Neutralisation of unfractionated (UF) heparins:

1mg of protamine sulphate will usually neutralise at least 100 international units of mucous heparin or 80 units of lung heparin. The dose of protamine sulphate should be reduced if more than 15 minutes have elapsed since intravenous injection.

For example, if 30-60 minutes have elapsed since heparin was injected intravenously, 0.5-0.75mg protamine sulphate per 100 units of mucous heparin is recommended. If two hours or more have elapsed, 0.25-0.375mg per 100 units of mucous heparin should be administered.
If the patient is receiving an intravenous infusion of heparin, the infusion should be stopped and 25-50mg of protamine sulphate given by slow intravenous injection.

If heparin was administered subcutaneously, 1mg protamine sulphate should be given per 100 units of mucous heparin - 25-50mg by slow intravenous injection and the balance by intravenous infusion over 8-16 hours.

In the reversal of UF heparin following cardiopulmonary bypass, either a standard dose of protamine may be given, as above, or the dose may be titrated according to the activated clotting time.

Patients should be carefully monitored using either the activated partial thromboplastin time or the activated clotting time, carried out 5-15 minutes after protamine sulphate administration. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin.

Neutralisation of low molecular weight (LMW) heparins:

A dose of 1mg per 100 units is usually recommended but the manufacturer's own guidelines should be consulted.

The anti-Xa activity of LMW heparins may not be completely reversible with protamine sulphate and may persist for up to 24 hours after administration.

The longer half-life of LMW heparins (approximately twice that of UF heparin) 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 heparin dose.

Theoretically, the dose of protamine sulphate should be halved when one half-life has elapsed since the last LMW heparin dose. Intermittent injections or continuous infusion of protamine sulphate have been recommended for the neutralisation of LMW heparin following subcutaneous administration, as there may be continuing absorption from the subcutaneous depot.

Patients should be carefully monitored. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin, especially low molecular weight heparin.

*Elderly:*

There is no current evidence for alteration of the recommended dose.

*Children:*

Safety and efficacy in children have not been established. Not recommended.

4.3 Contraindications

None known.
4.4 Special warnings and precautions for use
Too rapid administration of protamine sulphate may cause severe hypotension and anaphylactoid reactions. Facilities for resuscitation and treatment of shock should be available.

Protamine sulphate is not suitable for reversing the effects of oral anticoagulants. Caution should be observed when administering protamine sulphate to patients who may be at increased risk of allergic reaction to protamine. These patients include those who have previously undergone procedures such as coronary angioplasty or cardio-pulmonary by-pass which may include use of protamine, diabetics who have been treated with protamine insulin, patients allergic to fish and men who have had a vasectomy or are infertile and may have antibodies to protamine.

Patients undergoing prolonged procedures involving repeated doses of protamine should be subject to careful monitoring of clotting parameters. A rebound bleeding effect may occur up to 18 hours post-operatively which responds to further doses of protamine.

4.5 Interaction with other medicinal products and other forms of interaction
None known.

4.6 Fertility, pregnancy and lactation
As with most drugs, to be used only if clearly indicated in pregnancy and with caution during lactation.

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

4.8 Undesirable effects
Blood and lymphatic system disorders: anticoagulant effect (when used at doses in excess of that required to neutralise the anticoagulant effect of heparin).

Immune system disorders: Hypersensitivity reactions, including angioedema anaphylactoid reactions and fatal anaphylaxis, have been reported.

Cardiac disorders: bradycardia

Vascular disorders: sudden fall in blood pressure, pulmonary and systemic hypertension, transitory flushing and a feeling of warmth, severe, acute pulmonary vasoconstriction with cardiovascular collapse.

Respiratory, thoracic and mediastinal disorders: Dyspnoea. There have been rare instances of noncardiogenic pulmonary oedema with prolonged hypotension, with significant morbidity and mortality.

Gastrointestinal disorders: nausea and vomiting
Musculoskeletal and connective tissue disorders: back pain

General disorders and administration site conditions: lassitude

4.9 Overdose
Symptoms:- Protamine has weak anticoagulating properties and if given in the absence of heparin, or at doses in excess of those required to neutralise the anticoagulant effect of heparin, exerts its own anticoagulant effect.

Hypotension, bradycardia, dyspnoea, nausea, vomiting, lassitude, transitory flushing and/or a sensation of warmth may also occur.

Treatment:- Includes monitoring of coagulation tests, respiratory ventilation and symptomatic treatment. If bleeding is a problem, fresh frozen plasma or fresh whole blood should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antidotes, ATC Code: V03AB14

Although protamine is a potent antidote for heparin, its precise mechanism of action is unknown. However, when the strongly basic protamine combines with the strongly acid heparin, a stable salt is formed lacking in anticoagulant activity. 1mg of protamine sulphate neutralises between 80 and 120 units of heparin. However, methods of standardisation and the use of heparin from different sources (mucosal, lung) may produce different responses to protamine.

5.2 Pharmacokinetic properties
The onset of action of protamine occurs within five minutes following intravenous administration. The fate of the protamine-heparin complex is unknown, but it may be partially degraded, thus freeing heparin.

5.3 Preclinical safety data
No data are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride
Hydrochloric Acid 3M
Sodium Hydroxide 3M
Water for Injections
6.2 **Incompatibilities**
Protamine sulphate is incompatible with certain antibiotics, including several cephalosporins and penicillin.

6.3 **Shelf life**
48 months

6.4 **Special precautions for storage**
Store between 15°C and 25°C.

6.5 **Nature and contents of container**
5ml and 10ml neutral type 1 hydrolytic glass ampoules in pack sizes of 10 ampoules in cartons.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
U.K.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0520

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
08/03/2013

10 **DATE OF REVISION OF THE TEXT**
08/03/2013
Prosluf 10mg/ml solution for injection
(protamine sulphate)
PL 29831/0520

Patient Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

PROSULF 10mg/ml Solution for Injection
(PROTAMINE SULPHATE)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again while you are receiving your treatment.
- If you have any further questions, please ask your doctor or nurse.
- This medicinal product has been prescribed for you. The contents of this leaflet should not be shared with other patients.

In this leaflet:

1. What PROSULF is and what it is used for
2. How to take PROSULF
3. How much PROSULF should be given
4. Possible side effects
5. How to store PROSULF
6. Further information

1. What PROSULF is and what it is used for

The name of your medicine is PROSULF. The active ingredient is Protamine Sulfate.

How does this medicinal work?
PROSULF contains protamine sulfate which is a long-acting anticoagulant which reverses the anti-blood-clotting effect of heparin and prevents it from thinning the blood too much.

It is used before surgery, after medical treatment or when:
- heart surgery, if you have had a heart procedure before or if this heart procedure has been given to you by another doctor.

2. How to take PROSULF

PROSULF should only be given as an antidote to heparin. It is not suitable for use as an antidote to other medications that are used to thin the blood that are taken by mouth.

PROSULF should not be used if you have ever had a reaction or have been told that you are allergic to protamine sulfate or any of the other ingredients in the injection (see list under ‘What PROSULF contains in section is of this leaflet’).

3. How much PROSULF should you be given

PROSULF should only be given as an antidote to heparin. It is not suitable for use as an antidote to other medications that are used to thin the blood that are taken by mouth.

PROSULF should not be used if you have ever had a reaction or have been told that you are allergic to protamine sulfate or any of the other ingredients in the injection (see list under ‘What PROSULF contains in section is of this leaflet’).

1. NAME OF THE MEDICINAL PRODUCT
PROSULF 10mg/ml Solution for Injection
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Protamine Sulfate (10mg/ml).
3. PHARMACOTHERAPEUTIC FORM
Solution for injection.
4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Protamine sulfate is used to counteract the anticoagulant effect of heparin before surgery, after medical treatment or after heart surgery.

4.2 Pharmacology and method of administration
Adults
PROSULF should be administered by slow intravenous injection over a period of about 5 to 10 minutes. No more than 50mg of protamine sulfate should be given in any one dose.

The dose is dependent on the amount and type of heparin to be neutralized, the mode of administration, and the time elapsed since it was given and the degree of coagulation to be maintained. Usually, the dose required to neutralize the action of heparin should be guided by coagulation studies or calculated from a protamine neutralization test.

In general, protamine sulfate is given until a normal clotting time is obtained.

Neutralization of unfractionated heparin:
A dose of 100 mg of protamine sulfate per 1000 units of unfractionated heparin on an injection over a period of 5 to 10 minutes is usually adequate.

Neutralization of low molecular weight LMW heparin:
A dose of 50 mg of protamine sulfate per 1000 units of LMW heparin on an injection over a period of 5 to 10 minutes is usually adequate.

Elderly:
There is limited evidence for the administration of the recommended dose.

Children:
Safety and efficacy in children have not been established. Non-recommended.

4.3 Overdosed effects
None known.

4.4 Special warnings and precautions for use

The rapid administration of protamine sulfate may cause severe hypotension and arrhythmias requiring treatment. Facilities for resuscitation and treatment of shock should be available.

Protamine sulfate is not suitable for reversing the effects of oral anticoagulants.

4.5 Concomitant use

Patients who have received heparin and are also taking aspirin or other non-steroidal anti-inflammatory drugs are at increased risk of adverse reactions to protamine.

In patients who take aspirin, there is a 10 to 20% risk of cardiovascular death, which may include use of aspirin, clopidogrel and other antithrombotic drugs.
No more than 50 milligrams of prostanide sulphate should be given to you as a dose. Your doctor will decide the dose that is best for you.

If you do not understand, or are in any doubt, ask your doctor or nurse.

If you think you have received a dose more than you were told to take, or you are feeling unwell, ask your doctor or nurse for advice.

If you think you have been given too much Prosulf®, if you think you have been given the wrong Prosulf®, speak to your doctor or nurse. Signs of an overdose include hypotension (a lowering of blood pressure), an abnormally slow heart rate, a shortness of breath, increasing unsteadiness, breathing difficulty, feeling sick, feeling dizzy, a feeling of weakness or fainting and/or a feeling of warmth.

4. POSSIBLE SIDE EFFECTS

Unlike many medicines, Prosulf® may cause side-effects in some patients, particularly when it is first given. These include:

- dizziness of the pulse
- low blood pressure (you may feel dizzy or faint or you may black out)
- high blood pressure
- shortness of breath
- twisting and a feeling of warmth in the body
- back pain
- feeling sick
- tingling
- tiredness

Tiredness, allergic reactions or itching resulting in breathing difficulty or rash. This can sometimes be more serious with itching and swelling of the face and hands, and a blue discoloration of the fingernails. The doctor treating you will ready to treat these effects if they occur.

If you experience any other side-effects or feel that the medicine is affecting you badly, tell your doctor or nurse immediately.

5. HOW TO STORE PROSULF®

Keep out of reach of children.

Prosulf® should not be used if the expiry date on the label has passed. The expiry date refers to the last day of that month.

6. PHARMACOLOGICAL PROPERTIES

6.1 Pharmacological properties

Prostanide sulphate is a potent antagonist for humans. It has a direct effect on the smooth muscle of blood vessels, particularly the coronary arteries, and the renal vessels. It relaxes all smooth muscle in the body, including the smooth muscle in the walls of blood vessels, including those in the coronary arteries, the pulmonary system, and the renal arteries. It also relaxes smooth muscle in the walls of the airways, and in the gastrointestinal tract.

6.2 Interactions with other medicinal products

Do not use Prosulf® with other medicines that have a similar action or that could cause a similar effect. This includes other medicines that have an anticoagulant effect or that are used to treat high blood pressure.

6.3 Preclinical safety data

No data are available.

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

- Sodium bicarbonate
- Hydrochloric acid 3M
- Sodium hydroxide 3M
- Water for injection

7.2 Impossibility

Prosulf® is incompatible with certain medicines, including some anaesthetics and anticoagulants.

7.3 Shelf life

48 months.

7.4 Special precautions for storage

Store below 15°C and 25°C.

7.5 Nature and contents of container

30ml and 30ml glass vials containing 100 units of prosulfan in 100 units of sodium bicarbonate.

7.6 Special precautions for disposal

Not applicable.

8. MARKETING AUTHORITY HOLDER

Weikerts-WRL Ltd
Ash Road North, Wednesfield, Wolverhampton, WLL13 9RJ, UK

9. MARKETING AUTHORITY NUMBER(S)

PL 29861 (138290)

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

UK: August 2012
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11. DATE OF REVISION OF THE TEXT

August 2012
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Labelling