Package leaflet: Information for the user

PROSULF® 10mg/ml Solution for Injection

(PROTAMINE SULFATE)

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.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Prosulf®10mg/ml Solution for Injection. In the rest of this leaflet, it is called Prosulf®.

What is in this leaflet

1. What Prosulf® is and what it is used for

The name of your medicine is Prosulf®. The active ingredient in Prosulf® is protamine sulfate.

Prosulf® contains protamine sulfate which is a heparin antidote which neutralises the anti blood-clotting effect of heparin and prevents it from thinning the blood too much.

It is used before surgery, after kidney dialysis, after open-heart surgery, if you bleed during heparin treatment or if too much heparin has been given to you by accident.

2. What you need to know before you use Prosulf®

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

Do not use Prosulf®:

- if you are allergic to protamine sulfate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist or nurse before using Prosulf® if you:

- are allergic to fish, because you may also be allergic to Prosulf® as protamine sulfate comes from fish.
- have ever had heart surgery
- are an insulin dependent diabetic because Prosulf® may cause problems if you have previously used protamine insulin
- are a man and you have had a vasectomy or are infertile.

If you are undergoing a long operation, where repeated doses of Prosulf® are necessary, you may occasionally experience bleeding up to 18 hours after your operation, which will stop when you are given further doses of Prosulf®.

If any of the above apply to you, speak to your doctor or nurse before Prosulf® is given to you.

Other medicines and Prosulf®

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those medicines obtained without a prescription.

Pregnancy and breast-feeding

You should let your doctor know if you are pregnant or breast-feeding before Prosulf® is administered.

Driving and using machines

Prosulf® has not been reported to affect ability to drive or operate machines.

Prosulf® contains sodium

This medicine contains less than 1 mmol sodium (23mg) per 10mg/ml, that is to say essentially 'sodium- free'.

3. How to use Prosulf®

Do not use in children aged 12 years or younger.

- Blood clotting tests should be carried out to check on the effects of Prosulf® to see if you need further doses.
- Prosulf® should be given slowly by infusing into a vein over a period of about ten minutes.
- The dose of Prosulf® you will be given depends on the amount and type of heparin to be neutralised, the way the heparin was given to you, and the amount of time that has passed since your last heparin injection.
- No more than 50 milligrams protamine sulfate should be given to you in one 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.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prosulf® 10mg/ml Solution for Injection
Protamine Sulfate 10mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Protamine Sulfate 10mg/ml.

3 PHARMACEUTICAL FORM

Solution for injection
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Protamine sulfate 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 sulfate 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 sulfate will usually neutralise at least 100 international units of mucous heparin or 80 units of lung heparin. The dose of protamine sulfate 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 sulfate 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 sulfate given by slow intravenous injection.

If heparin was administered subcutaneously, 1mg protamine sulfate 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 sulfate 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 sulfate 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 sulfate required in relation to the time which has elapsed since the last heparin dose.

Theoretically, the dose of protamine sulfate should be halved when one half-life has elapsed since the last LMW heparin dose. Intermittent injections or continuous infusion of protamine sulfate 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 sulfate may cause severe hypotension and anaphylactoid reactions. Facilities for resuscitation and treatment of shock should be available.

Protamine sulfate is not suitable for reversing the effects of oral anticoagulants. Caution should be observed when administering protamine sulfate 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

If you forget to use Prosulf®

If you think that an injection has been missed, speak to your doctor or nurse.

Do not use a double dose to make up for a forgotten dose.

If you use more Prosulf® than you should
If you think you have been given too much 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, excessive/ unexplained bleeding and/or bruising, feeling sick, being sick, a feeling of weakness or facial flushing and/or a feeling of warmth.

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

4. Possible side effects

Like all medicines, this medicine can cause side-effects particularly when it is first given, although not everybody gets them.

These include:
- slowing of the pulse
- low blood pressure (you may feel dizzy or faint or you may black out)
- high blood pressure
- shortness of breath
- flushing and a feeling of warmth in the body
- back pain
- feeling sick
- being sick
- tiredness

Rarely, allergic reactions occur resulting in breathing difficulties or a rash. This can sometimes be more serious with fainting and collapse, swelling of the lips and face, and a blue discoloration of the lips and tongue. The doctor treating you will be ready to treat these effects if they occur.

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 via the national reporting systems listed below:

United Kingdom:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta:
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prosulf®

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 label. The expiry date refers to the last day of that month.

Do not use this medicine if it is discoloured or has gone cloudy.

The injection should be stored between 15°C and 25°C in the package or container in which it was dispensed.

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 Prosulf® contains
The active ingredient in Prosulf® is protamine sulfate. The injection comes in one strength of 10mg/ml.

Other ingredients in Prosulf® injection are sodium chloride, water for injections and trace amounts of hydrochloric acid and sodium hydroxide.

What Prosulf® looks like and contents of the pack
Prosulf® is a clear and colourless solution for injection. It is available in packs of 10 glass ampoules. Each ampoule contains 5ml of solution.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

Manufacturer:
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

Other formats
To listen to or request a copy of this information in Braille, large print or audio please call, free of charge: **0800 198 5000 (UK only)**

Please be ready to give the following information:

Product name	Reference number
Prosulf® 10mg/ml Solution for Injection	PL 29831/0180

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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 to use machinery
None.

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

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:

UK - Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta - ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal.

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
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 sulfate 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 sulfate 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
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0180
MA154/02501

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 17 May 1991
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10 DATE OF REVISION OF THE TEXT
03/2018

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