

DATA SHEET

Product Summary

1. Trade Name of Medicinal Product

Protamine Sulphate Injection BP

2. Qualitative and Quantitative Composition

Protamine Sulphate 10mg/ml

3. Pharmaceutical Form

Solution for injection
A clear, colourless solution.

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:

Protamine sulphate 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.

Patients should be carefully monitored using either the activated partial thromboplastin time or the activated coagulation 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, especially low molecular weight heparin.

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.

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.

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 that 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 Medicaments

None known.

4.6 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

When used at doses in excess of that required to neutralise the anticoagulant effect of heparin, protamine sulphate exerts its own anticoagulant effect. Following injection of protamine sulphate the following effects have been observed; a sudden fall in blood pressure, bradycardia, pulmonary and systemic hypertension, dyspnoea, transitory flushing and a feeling of warmth, back pain, nausea and vomiting, lassitude. Hypersensitivity reactions, including angioedema and fatal anaphylaxis, have been reported. There have been rare instances of noncardiogenic pulmonary oedema with prolonged hypotension, with significant morbidity and mortality.

4.9 Overdose

Symptoms:- Overdosage may cause hypotension, bradycardia and dyspnoea with a sensation of warmth, nausea, vomiting, lassitude and transitory flushing.

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.

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 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 Pre-clinical safety data

No data are available.

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

36 months

6.4 Special Precautions for Storage

Store between 15°C and 25°C.

6.5 Nature and Contents of Container

5ml neutral type 1 hydrolytic glass ampoules in pack sizes of 10 ampoules in cartons.

6.6 Instructions for Use/Handling

Not applicable.

Administrative Data

7. Date of Preparation

27 November, 2001

8. New Zealand Distributor

Artex Limited
P O Box 249
Waipukurau

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