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# PROTAMINE SULFATE INJECTION, USP

## DESCRIPTION

Protamine Sulfate Injection, USP is a sterile, nonpyrogenic, isotonic solution of protamine sulfate in Water for Injection. It acts as a heparin antagonist. It is also a weak anticoagulant.

Protamines are simple protein principles obtained from the sperm of salmon and certain other species of fish. Protamines have low molecular weight, are rich in arginine, and are strongly basic.

Protamine sulfate occurs as fine white or off-white amorphous or crystalline powder. It is sparingly soluble in water. The pH is between 6 and 7. The cationic hydrogenated protamine at a pH of 6.8 to 7.1 reacts with anionic heparin at a pH of 5.0 to 7.5 to form an inactive complex.

**Each mL contains:**

Protamine sulfate 10 mg, sodium chloride 9 mg and Water for Injection q.s. Sulfuric acid and/or dibasic sodium phosphate (heptahydrate) may have been added for pH adjustment.

The preparation is preservative free.

Protamine sulfate is administered intravenously.

## CLINICAL PHARMACOLOGY

When administered alone, protamine has an anticoagulant effect. However, when it is given in the presence of heparin (which is strongly acidic), a stable salt is formed which results in the loss of anticoagulant activity of both drugs.

Protamine sulfate has a rapid onset of action.

Neutralization of heparin occurs within five minutes after intravenous administration. Although the metabolic fate of the heparin-protamine complex has not been elucidated, it has been postulated that protamine sulfate in the heparin-protamine complex may be partially metabolized or may be attacked by fibrinolysin, thus freeing heparin.

## INDICATIONS AND USAGE

Protamine Sulfate Injection, USP is indicated in the treatment of heparin overdosage.

## CONTRAINDICATIONS

Protamine sulfate is contraindicated in patients who have shown previous intolerance to the drug.

## WARNINGS

Hyperheparinemia or bleeding has been reported in experimental animals and in some patients 30 minutes to 18 hours after cardiac surgery (under cardiopulmonary bypass) in spite of complete neutralization of heparin by adequate doses of protamine sulfate at the end of the operation.

Therefore, it is important to keep the patient under close observation after cardiac surgery. Additional doses of protamine sulfate should be administered if indicated by coagulation studies, such as the heparin titration test with protamine and the determination of plasma thrombin time.

**Too-rapid administration of protamine sulfate can cause severe hypotensive and anaphylactoid-like reactions** (see **DOSAGE AND ADMINISTRATION**). Facilities to treat shock should be available.

## PRECAUTIONS

### General

**Because of the anticoagulant effect of protamine, it is unwise to give more than 100 mg over a short period unless there is certain knowledge of a larger requirement.**

Previous exposure to protamine through use of protamine-containing insulins or during heparin neutralization may predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug. Reports of the presence of antiprotamine antibodies in the serums of infertile or vasectomized men suggest that some of these individuals may react to the use of protamine sulfate.

Patients with a history of allergy to fish may develop hypersensitivity reactions to protamine, although to date no relationship has been established between allergic reactions to protamine and fish allergy.

### Drug Interactions

Protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins (see **DOSAGE AND ADMINISTRATION**).

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed to determine potential for carcinogenicity, mutagenicity or impairment of fertility.

### Usage In Pregnancy

Animal reproduction studies have not been conducted with protamine sulfate. It is also not known whether protamine sulfate can cause fetal harm when administered to a pregnant woman

or can affect reproduction capacity. Protamine sulfate should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when protamine sulfate is administered to a nursing woman.

**Usage in Children**

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Intravenous injections of protamine may cause a sudden fall in blood pressure, bradycardia, pulmonary hypertension, dyspnea, or transitory flushing and a feeling of warmth. There have been reports of anaphylaxis that resulted in respiratory embarrassment (see **PRECAUTIONS**). Other reported adverse reactions include systemic hypertension, nausea, vomiting and lassitude. Back pain has been reported rarely in conscious patients undergoing such procedures as cardiac catheterization. Because fatal reactions often resembling anaphylaxis have been reported after administration of protamine sulfate, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

## OVERDOSAGE

Because of the anticoagulant effect of protamine sulfate, overdosage of this drug may theoretically result in hemorrhage. However, in one study, overdosage of 600 to 800 mg of intravenous protamine sulfate had only minimal, transient effects on blood coagulation tests. The patient should be followed with coagulation studies and treated symptomatically.

The $LD_{50}$ of protamine sulfate is 100 mg/kg in mice.

## DOSAGE AND ADMINISTRATION

Each mg of protamine sulfate will neutralize approximately 90 USP units of heparin activity derived from beef lung tissue or about 115 USP units of heparin activity derived from porcine intestinal mucosa.

**Protamine Sulfate Injection, USP should be given by very slow intravenous injection in doses not to exceed 50 mg of protamine sulfate in any 10-minute period** (see **WARNINGS**).

Protamine sulfate is intended for injection without further dilution; however, if further dilution is desired, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection may be used. Diluted solutions should not be stored since they contain no preservative.

Protamine sulfate should not be mixed with other drugs without knowledge of their compatibility, because protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins.

Because heparin disappears rapidly from the circulation, the dose of protamine sulfate required also decreases rapidly with the time elapsed following intravenous injection of heparin. For example, if the protamine sulfate is administered 30 minutes after the heparin, one-half the usual dose may be sufficient. The dosage of protamine sulfate should be guided by blood coagulation studies (see **WARNINGS**). Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration, whenever solution and container permit.

## AVAILABILITY OF DOSAGE FORMS

**Product Number**

C22905 Protamine Sulfate Injection, USP
10 mg/mL, 5 mL single-dose, flip-top vials in packages of 25.

C22930 Protamine Sulfate Injection, USP
10 mg/mL, 25 mL fill in a 30 mL single-dose, flip-top vial, individually packaged.

Store at controlled room temperature between 15 and 30°C. Do not freeze.

**Note: The 25 mL vials are designed for antiheparin treatment in certain cases in which large doses of heparin have been given during surgery and are to be neutralized by large doses of protamine sulfate after surgical procedures.**

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