

Protosol

Proteinase inhibitor, for I.V. injection

COMPOSITION

Each ml contains:

aprotinin 10,000 KIU in a sterile isotonic solution.

The potency of aprotinin is expressed in terms of Kallikrein Inactivator Units (KIU) or of Trypsin Inhibitor Units (European Pharmacopoeia Units, each equivalent to 1800 KIU).

ACTION

Aprotinin is a single-chain polypeptide consisting of 58 amino acid residues, with a molecular weight of about 6500. It is derived from bovine lung tissue, from which it is extracted and purified using ion exchange chromatography and ultrafiltration. Aprotinin is an inhibitor of proteolytic enzymes. Its action may be used to advantage in the kinin system by inhibition of kallikrein (kallidinogenase) and trypsin, in the blood coagulation system by inhibition of plasmin, and the enzyme systems of leukocytes and damaged tissue cells by inhibition of lysosomal proteinases.

Following an intravenous injection of **Protosol**, aprotinin immediately distributes into the entire extra-cellular liquid space. Its concentration in the blood thus diminishes very rapidly. The plasma half-life after injection, following the initial plasma distribution, is about 2.5 hours. A second disappearance phase with a half-life of about 10 hours commences about 5 hours after administration.

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. Elimination of aprotinin is via the kidneys. It is excreted in the urine as inactive degradation products.

INDICATIONS

Protosol is used in the treatment and prophylaxis of disorders in which inhibition of proteolytic enzymes such as kallikrein, trypsin, plasmin, tissue and leukocyte proteinases, and plasma factors in the initial phase of coagulation, is indicated.

Protosol is indicated for the early treatment of the following states of shock:

- Traumatic shock and fat-embolism syndrome.
- Acute pancreatitis and pancreatogenic shock.
- Perforative peritonitis and prophylaxis of septic shock.
- Hemorrhagic shock and hemorrhages due to hyperfibrinolysis.

Protosol is also used for the prevention of the following post-operative or post-traumatic complications:

- Acute hemorrhagic pancreatitis.
- Pulmonary embolism.
- Aseptic wound healing disturbances.
- Local hemorrhages due to hyperfibrinolysis.
- Prophylaxis of abdominal adhesions.

Protosol is indicated as a supplement to, not a replacement for, the standard treatment modalities in the above conditions (e.g. volume substitution and oxygen in shock management).

Protosol is also indicated to reduce major blood loss in patients undergoing surgery involving cardiopulmonary bypass.

CONTRAINDICATIONS

Known hypersensitivity to aprotinin.

Patients with thromboembolic disease requiring anticoagulant therapy.

WARNINGS

Anaphylactic or anaphylactoid reactions have been reported on rare occasions. These may occur during or following an injection, either with the first dose or upon repetition of the treatment, when there has been an interval between courses of treatment. The risk of such reactions is increased if the injection, especially of a large dose, is administered too rapidly.

Apart from possible skin eruptions, symptoms include a rapid pulse, pallor or cyanosis, shortness of breath, increased perspiration and nausea.

Pre-treatment intraocular or intradermal challenge may be useful in identifying allergic patients. However, there has been at least one reported case of an anaphylactic reaction to aprotinin despite negative ocular sensitivity testing.

If a hypersensitivity reaction occurs, administration must be stopped immediately and appropriate intensive counteractive measures initiated. These include administration of adrenaline 0.05-0.1 mg i.v. (several times if

necessary), prednisolone 250-1000 mg i.v., and antihistamines. Intravenous fluids, bronchodilators and respiratory support may also be required.

Use in Pregnancy

Animal studies conducted with aprotinin have not revealed any evidence of teratogenicity or embryotoxicity. However, because of the lack of documented human experience, the use of **Protosol** during pregnancy, especially in the first trimester, should be restricted to those life-threatening cases in which the potential benefit to the patient outweighs the risk to the fetus.

Use in Breastfeeding

Due to the lack of evidence regarding possible effects on the nursing infant, if the potential benefit to the mother of **Protosol** treatment overrides the needs of the infant, it would appear to be prudent for the mother to discontinue breastfeeding.

ADVERSE REACTIONS

Protosol is usually well-tolerated.

Local thrombophlebitis may develop occasionally, as a result of administration through a peripheral line or following repeated injections. Local reddening at the injection site may occur, especially following repeated doses. This usually disappears within a few hours. Other adverse reactions include anaphylactic shock (see WARNINGS), erythema, urticaria, bronchospasm, skin eruptions, tachycardia, pallor or cyanosis, dyspnea, nausea and other gastrointestinal disturbances.

Thromboembolism

The potential for thrombotic events exists with aprotinin therapy.

Early formation of thrombi was observed on the pulmonary artery catheter of 3 cardiac surgery patients receiving high-dose aprotinin; thrombi were detected 45 to 55 minutes following catheter insertion.

However, heparin-coated catheters were not used in this study.

There are no other reports of thrombotic sequelae as a result of aprotinin therapy. However, studies are needed to more adequately define the risk of perioperative and postoperative thromboembolism, and potential effect on graft closure rates during surgery for myocardial revascularization, with this agent.

Until these data are available, continued use of normal heparin doses with **Protosol** during cardiac surgery has been suggested.

PRECAUTIONS

Particular caution should be taken when administering **Protosol** to patients with an allergic diathesis or hypersensitivity to drugs; preliminary administration of antihistamines may be indicated.

In consumptive coagulopathies at the stage of excessive fibrin deposition, therapeutic fibrinolysis should be considered as an alternative to the inhibitor treatment.

Caution should be taken also with patients with previous exposure to aprotinin (increased risk of hypersensitivity) and patients with renal insufficiency.

Laboratory Parameters

The following should be monitored before and during bypass procedures: bleeding time, platelet counts, prothrombin time, activated clotting time, red blood cell counts, leukocyte counts, hematocrit, hemoglobin, fibrinogen degradation products.

Physical Examination

A "drier" operative field, minimal blood loss, and a low requirement for transfusion are characteristic of a response to aprotinin during cardiac surgery.

DRUG INTERACTIONS

a. Heparin

Protosol may prolong the activated clotting time (ACT) when performed to evaluate patients receiving heparin. This occurs when using a celite surface activation method; the ACT using kaolin is much less affected. Therefore, when evaluating heparinized patients receiving **Protosol**, the manufacturer of the ACT test should be consulted regarding its use and interpretation in these patients.

b. Succinylcholine

Aprotinin is a weak inhibitor of plasma pseudocholinesterase.

Concomitant administration of aprotinin and succinylcholine and tubocurarine has been reported to produce prolonged or recurring apnea in 3 cases.

DOSAGE AND ADMINISTRATION

Protosol must be administered slowly (maximum 5ml/min) by intravenous injection or as a short infusion. Patients must be in the supine position during administration.

To achieve maximum efficacy, because enzyme effects usually occur as immediate reactions to trauma or shock, initiation of **Protosol** therapy must begin as early as possible, in sufficient dosage (so that the ratio of the enzyme to the inhibitor is shifted in favor of the inhibitor), and for a sufficient period of time. Proteinases are often capable of autocatalytic activation, and can easily support a proteolytic process or restart one.

Activation of the coagulation system may require concomitant administration of **Protosol** with heparin.

The duration of **Protosol** treatment is guided by the clinical picture and the results of laboratory determinations (e.g. lipase, blood lipid fractions, electrolytes, oxygen saturation, metabolic products, partial thromboplastin time, fibrin monomers). In principle, however, since **Protosol** is indicated for the treatment of acute conditions and for short-term prophylaxis, duration of use should not normally exceed 7 days.

Cardiac Surgery

Following induction of anesthesia but prior to incision or reopening of a previous median sternotomy, administer 2,000,000 KIU as an i.v. loading dose. As recommended for other indications, the first 50,000 KIU should be administered slowly, over a period of several minutes, to minimize the risk of hypersensitivity reactions. The remainder of the loading dose is then given over a period of 20 minutes by slow i.v. injection or by infusion.

This is followed by a continuous infusion of 500,000 KIU/hr until skin closure at the end of the operation. In patients undergoing heart valve replacement for infective endocarditis, this maintenance dose may be continued into the early postoperative period.

An additional dose of 2,000,000 KIU may be introduced to the prime volume of the oxygenator, or 500,000 KIU may be added to each liter of whole blood given during the operation.

Early Treatment of Hemorrhagic States

In the treatment of hemorrhages until bleeding has been definitely controlled, first administer 500,000 KIU as a slow i.v. injection or by infusion; subsequently administer 200,000 KIU every 4 hours by slow i.v. injection.

When treating major obstetric and gynecological hemorrhages, higher doses may be required. Administer initially 1,000,000 KIU, followed by 200,000 KIU hourly until the bleeding stops. For the treatment of local hyperfibrinolytically-determined hemorrhages in obstetrics and gynecology, an immediate slow i.v. injection of 200,000 KIU, followed by 100,000 KIU hourly until the bleeding stops, is effective.

Prophylaxis of Postoperative or Post-traumatic Complications

At the start of treatment, or with the induction of anesthesia, administer 200,000 KIU by slow i.v. injection, followed by 100,000 KIU every 6 hours by slow i.v. injection, up to and including the second postoperative day.

For the prevention of local hyperfibrinolytically-determined hemorrhages in obstetrics and gynecology, 200,000 KIU as an infusion is effective.

In order to prevent adhesion of the abdominal wall following surgery, introduce 500,000 KIU (50,000 KIU in neonates and infants up to 3 months) into the abdominal cavity before closure.

Children

Dosage in children is adjusted according to body weight, generally 20,000 KIU/kg/day.

PHARMACEUTICAL PRECAUTIONS

Immediately prior to administration, the contents of the vial should be inspected for particulate matter. The vial must not be used if its contents are cloudy or contain a precipitate. Once a vial has been opened, it should be used immediately. The vial is to be considered as a single-dose container: any unused portion should be discarded.

Except for electrolyte and sugar solutions, **Protosol** is incompatible with most drugs including corticosteroids, heparin, nutrient solutions containing amino acids or fat emulsions and tetracyclines.

Administration of **Protosol** in mixed infusions (particularly with β -lactam antibiotics) should be avoided.

PRESENTATION

Vial of 10 ml containing aprotinin 100,000 KIU

Vial of 50 ml containing aprotinin 500,000 KIU

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