Trasylol® 500,000 KIU

Active ingredient: aprotinin **Infusion solution**

Composition

1 vial of 50 mL contains aprotinin concentrated solution, corresponding to 500,000 KIU (Kallikrein-Inhibitor Units), in sterile isotonic sodium chloride solution.

500,000 KIU (approx. 70 mg aprotinin) corresponds to 277.8 Eur.Ph.Units.

Aprotinin is a colorless clear solution for infusion.

Description

Aprotinin is a highly purified natural proteinase inhibitor obtained from bovine lungs. It is made up of 58 amino acid residues that are arranged in a single polypeptide chain, cross-linked by three disulfide bridges. It has a molecular weight of 6512 daltons and a chemical formula of $C_{284}H_{432}N_{84}O_{79}S_7$. It is supplied as a clear, colorless, sterile isotonic solution for intravenous administration. Each milliliter contains 10,000 KIU (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5-6.5.

INDICATIONS

Aprotinin is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion.

CONTRAINDICATIONS

Hypersensitivity to aprotinin.

Patients with a positive aprotinin-specific IgG antibody test are at an increased risk of anaphylactic reaction when treated with aprotinin. Therefore, administration of aprotinin is contraindicated in these patients.
In case no aprotinin specific IgG antibody test is possible prior to treatment, administration of aprotinin to patients with a suspected previous exposure during the last 12 months is contraindicated.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Animal experiments did not provide any evidence of teratogenic or other embryotoxic effects of aprotinin.
Aprotinin should be used throughout pregnancy only if the potential benefit justifies the potential risk. In case of severe adverse drug reactions (like anaphylactic reaction, heart arrest, etc.) and their consecutive therapeutic measures, damage to the fetus has to be taken into account for a risk/benefit evaluation.

Lactation

It is not known whether aprotinin is excreted in human milk.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Aprotinin should be used throughout pregnancy only if the potential benefit justifies the potential risk (see “Pregnancy and Lactation”).

Hypersensitive reactions
Anaphylactic or anaphylactoid reactions have occurred with Trasylol administration, including fatal reactions in association with the initial (test) dose. The initial (test) dose does not fully predict a patient's risk for a hypersensitivity reaction, including a fatal reaction. Fatal hypersensitivity reactions have occurred among patients who tolerated an initial (test) dose (see also section on “Undesirable Effects”).

Hypersensitivity reactions often manifest as anaphylactic/anaphylactoid reactions with hypotension the most frequently reported sign of the hypersensitivity reaction. The hypersensitivity reaction can progress to anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol, administration should be stopped immediately and emergency treatment should be initiated. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

Trasylol should be administered only in operative settings where cardiopulmonary bypass can be rapidly initiated. Before initiating treatment with Trasylol, the recommendations below should be followed to manage a potential hypersensitivity or anaphylactic reaction: 1) Have standard emergency treatments for hypersensitivity or anaphylactic reactions readily available in the operating room (e.g., epinephrine, corticosteroids). 2) Administration of the initial (test) dose and loading dose should be done only when the patient is intubated and when conditions for rapid canulation and initiation of cardiopulmonary bypass are present. 3) Delay the addition of Trasylol into the pump prime solution until after the loading dose has been safely administered.

Re-exposure to aprotinin

Administration of Trasylol, especially to patients who have received aprotinin in the past requires a careful risk/benefit assessment because an allergic reaction may occur (see “Contraindications” and “Undesirable Effects”).
Aprotinin may also be a component of some fibrin sealant products and the use of these products should be included in the patient history.
Although the majority of cases of anaphylaxis occur upon re-exposure within the first 12 months, there are also single case reports of anaphylaxis occurring upon re-exposure after more than 12 months.
Standard emergency treatment for allergic/anaphylactic reactions should be readily available during treatment with aprotinin.

All patients treated with aprotinin should first receive a test dose to assess the potential for allergic reactions (see also section “Method of administration”). Before administration of the aprotinin test dose patients should be intubated and the facilities for rapid cannulation should be available in order to place the patient on extracorporeal circulation if required. The test dose should only be administered in the operation room.

Initial (test) dose:

A 1 mL (10,000 KIU) test dose of Trasylol should be administered to all patients with an observation time of at least another 10 minutes before the loading dose of Trasylol is given as described under section “Posology and Method of Administration”. A H_1-antagonist and a H_2-antagonist may be administered 15 minutes prior to the test dose of aprotinin.

However, even after the uneventful administration of the initial 1 mL test dose, the therapeutic dose may cause an anaphylactic reaction. If this happens, the infusion of aprotinin should immediately be stopped, and the standard emergency treatment for anaphylaxis be applied, if necessary.

Renal dysfunction

An increase in renal failure and mortality compared to age-matched historical controls has been reported for aprotinin-treated patients undergoing cardiopulmonary bypass with deep hypothermic circulatory arrest during operation of the thoracic aorta. Trasylol should therefore be used with extreme caution under these circumstances. Adequate anti-coagulation with heparin must be assured (see also additional note below).

Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period. This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function. Data from Bayer's global pool of placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) surgery showed that the incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher at 9.0% (185/2047) in the high-dose aprotinin (Regimen A) group compared with 6.6% (129/1957) in the placebo group. In the majority of instances, post-operative renal dysfunction was not severe and was reversible. However, renal dysfunction may progress to renal failure and the incidence of serum creatinine elevations >2.0 mg/dL above baseline was slightly higher in the high-dose aprotinin group (1.1% vs. 0.8%). Careful consideration of the balance of risks and benefits is therefore advised before administration of Trasylol to patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides or products that alter renal function).

Additional note on use with extracorporeal circulation

In patients undergoing cardiopulmonary bypass with aprotinin therapy, one of the following methods is recommended to maintain adequate anticoagulation:

1) Activated Clotting Time (ACT)
An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth-based (celite) ACTs. While protocols vary, a minimal celite-ACT of 750 seconds or kaolin-ACT of 480 seconds, independent of the effects of haemodilution

and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of aprotinin.

2) Fixed Heparin Dosing
A standard loading dose of heparin, administered prior to cannulation of the heart, plus the quantity of heparin added to the prime volume of the cardiopulmonary bypass circuit, should total at least 350 IU/kg. Additional heparin should be administered in a fixed-dose regimen based on patient weight and duration of cardiopulmonary bypass.

3) Determination of Heparin Levels
Protamine titration, a method that is not affected by aprotinin, can be used to measure heparin levels. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose. Additional heparin should be administered on the basis of heparin levels measured by protamine titration. Heparin levels during bypass should not be allowed to drop below 2.7 U/mL (2.0 mg/kg) or below the level indicated by heparin dose-response testing performed prior to administration of aprotinin.

In aprotinin treated patients the neutralization of heparin by protamine after discontinuation of cardiopulmonary bypass should either be based on a fixed ratio to the amount of heparin applied or be controlled by a protamine titration method.

Important: Trasylol is not a heparin-sparing agent.

UNDESIRABLE EFFECTS

Allergic/anaphylactic reactions are rare in patients with no prior exposure to aprotinin. In case of re-exposure the incidence of allergic/anaphylactic reactions may reach the five percent level. A retrospective review showed that the incidence of an allergic/ anaphylactic reaction following re-exposure is increased when the re-exposure occurs within 6 months of the initial administration (5.0 % for re-exposure within 6 months and 0.9 % for re-exposures greater than 6 months). A retrospective review suggests that the incidence of severe anaphylactic reactions to aprotinin may further increase when patients are re-exposed more than twice within 6 months. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe allergic reactions or anaphylactic shock with, in very rare cases, fatal outcome.

The symptoms of allergic/anaphylactic reactions may include:

Respiratory system:	asthma (bronchospasm)
Cardiovascular system:	hypotension
Skin and appendages:	pruritus, rash, urticaria
Digestive system:	nausea

If allergic reactions occur during injection or infusion, administration should be stopped immediately. Standard emergency treatment may be required, i.e. adrenaline/epinephrine, volume substitution and corticosteroids.

Cardiovascular system:

In the pooled analysis of all placebo-controlled clinical studies, the incidence of investigator-reported myocardial infarction (MI) in aprotinin treated patients was 5.8% compared to 4.8% in placebo treated patients, with difference of 0.98% between the groups (aprotinin n=3817 and placebo n=2682; status: April 2005).

A trend of increased incidence of MI in association with aprotinin was observed in some studies, while other studies showed a lower incidence compared to placebo.

In a multi-centre study in patients undergoing primary coronary artery bypass graft surgery there was an increased risk of graft closure (coronary occlusion) for Trasylol treated patients compared to patients who received placebo. This result was mainly negatively influenced by two centres. Subanalysis clearly demonstrated that for one centre inadequate heparinisation was the primary issue while the other centre used a non-standard graft conservation technique. In addition to the note on heparinisation (see "Precautions for use") the practice of using blood from the aprotinin central infusion line is strongly discouraged. No differences between the treatment groups were observed for the incidence of myocardial infarctions or of deaths in this study.

Adverse drug reactions (ADRs) based on all placebo-controlled clinical studies with aprotinin sorted by CIOMS III categories of frequency (aprotinin n=3817 and placebo n=2682; status: April 2005) are listed below:

ADRs derived from post marketing reports (n=584 reports, status: April 2005) are printed in bold italic in the tabulated version

Clinical Description	**Common** ≥1% to <10%	**Uncommon** ≥0.1% to <1%	**Rare** ≥0.01% to <0.1%	**Very Rare** <0.01%
General Disorders or Administration Site Conditions				
Infusion site reactions				Injection and infusion site reactions Infusion site (thrombo-) phlebitis
Cardiac Disorders				
Myocardial disorders		Myocardial ischemia Coronary occlusion/ thrombosis Myocardial infarction		
Pericardial effusion		Pericardial effusion		
Vascular Disorders				
Embolism and thrombosis		Thrombosis	Arterial thrombosis (and its organ-specific manifest-ations that might occur in vital organs such as kidney, lung or brain)	***Pulmonary embolism***
Blood and Lymphatic System Disorders				
Changes in coagulation				***Disseminated intravascular coagulation*** ***Coagulopathy***

Immune System Disorders				
Acute hypersensi-tivity reactions			Allergic reaction Anaphylactic / anaphylactoid reaction	***Anaphylactic shock (potentially life threatening)***
Renal and Urinary Disorders				
Renal impairment		Oliguria, acute renal failure, renal tubular necrosis		

OVERDOSE

There is no specific antidote.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Trasylol has a dose-dependent inhibitory effect on the action of thrombolytic agents, e.g. streptokinase, urokinase, alteplase (r-tPA).

POSOLOGY AND METHOD OF ADMINISTRATION

Dosage:

An appropriate aprotinin-specific IgG antibody test should be performed in all patients before administration of aprotinin (see "Contraindications").

The following dose regimen is recommended for adult patients:
Owing to the risk of allergic/anaphylactic reactions, a 1 mL (10,000 KIU) test dose should be administered to all patients at least 10 minutes prior to the remainder of the dose. After the uneventful administration of the 1 mL test dose, the therapeutic dose may be given. A H_1-antagonist and a H_2-antagonist may be administered 15 minutes prior to the test dose of aprotinin. In any case standard emergency treatments for anaphylactic and allergic reactions should be readily available (See "Warnings and Precautions for use").

In general, the total amount of aprotinin administered per treatment course should not exceed 7 million KIU.

Method of administration:

All intravenous doses of aprotinin should be administered through a central venous line. Do not administer any other drug using the same line.

Aprotinin must be given only to patients in the supine position and must be given slowly (maximum 5-10 mL/min) as an intravenous injection or a short infusion.

A loading dose of 1-2 million KIU is administered as a slow intravenous injection or infusion over 20-30 minutes after induction of anaesthesia and prior to sternotomy. A further 1-2 million KIU should be added to the "pump prime" of the heart-lung machine. To avoid physical incompatibility of aprotinin and heparin when adding to the pump prime solution, each agent must be added during recirculation of the pump prime to assure adequate dilution prior to admixture with the other component.
The initial bolus infusion is followed by the administration of a continuous infusion of 250,000 – 500,000 KIU per hour until the end of the operation.

Patients with renal impairment: Clinical experience so far suggests that patients with decreased renal function do not require special dose adjustment.

Pediatric use: Infants, toddlers, children, and adolescents: efficacy and safety have not been established in this patient population.

Geriatric use: Reported clinical experience has not identified differences in responses in elderly patients.

PHARMACODYNAMIC PROPERTIES

Aprotinin is a broad spectrum protease inhibitor which has antifibrinolytic properties. By forming reversible stoichiometric enzyme-inhibitor complexes, aprotinin acts as an inhibitor of human trypsin, plasmin, plasma kallikrein and tissue kallikrein, thus inhibiting fibrinolysis.
It also inhibits the contact phase activation of coagulation which both initiates coagulation and promotes fibrinolysis. In the special situation of cardiopulmonary bypass and foreign-surface mediated contact activation, additional inhibition of plasma kallikrein appears to contribute to the desired effect, which in general can be described as minimising derangements in the coagulation and fibrinolysis system.
Aprotinin modulates the systemic inflammatory response (SIR) associated with cardiopulmonary bypass (CPB) surgery. SIR results in the interrelated activation of the hemostatic, fibrinolytic, cellular and humoral inflammatory systems. Aprotinin, through its inhibition of multiple mediators (e.g., kallikrein, plasmin, trypsin) results in the attenuation of inflammatory responses, fibrinolysis, and thrombin generation. Aprotinin has a dose-dependent inhibitory effect on the action of thrombolytic agents (ie streptokinase, tPA and urokinase)
Aprotinin inhibits pro-inflammatory cytokine release and maintains glycoprotein homeostasis. In platelets, aprotinin reduces glycoprotein loss (e.g., GpIb, GpIIb/IIIa), while in granulocytes it prevents the expression of pro-inflamma-tory adhesive glycoproteins (e.g., CD11b).
The effects of aprotinin use in cardiopulmonary bypass surgery (CPB) involves a reduction in inflammatory response which translates into a decreased need for allogenic blood transfusions, reduced bleeding, and decreased mediastinal re-exploration for bleeding.

PHARMACOKINETIC PROPERTIES

After intravenous injection, rapid distribution of aprotinin occurs into the total extracellular space, leading to an initial decrease in plasma aprotinin concentration with a half-life of 0.3-0.7 h. At later time points, (i.e. beyond 5 hours post-dose) there is a terminal elimination phase with a half-life of about 5-10 hours.

Average steady state intraoperative plasma concentrations were 175 - 281 KIU/mL in patients treated with aprotinin during cardiac surgery by administration of the following dosage regimen: 2 million KIU as intravenous loading dose, 2 million KIU into the pump prime volume, 500,000 KIU per hour of operation as continuous intravenous infusion. Average steady state intraoperative plasma concentrations were 110 - 164 KIU/mL after administration of half of that regimen.

The studies comparing the pharmacokinetics of aprotinin in healthy volunteers, cardiac patients undergoing cardiopulmonary bypass, and women undergoing hysterectomy, suggest linear pharmacokinetics over the dose range of 50,000 KIU to 2 million KIU.

The binding of aprotinin to plasma protein was determined ex vivo in rat plasma by using an ultracentrifugation method. Approx. 20% of the anti-fibrinolytic activity was found unbound in the protein-free layer whereas 80% were associated to plasma proteins.

The steady state volume of distribution was about 20 l and the total body clearance was approx. 40 mL/min in man.

Aprotinin accumulates in the kidneys and to a lesser degree also in cartilaginous tissue. Enrichment in the kidneys is due to binding to the brush border of the epithelial cells of the proximal tubules and enrichment in the phagolysosomes of these cells. Accumulation in the cartilaginous tissue results from the affinity of the basic aprotinin to the acid proteoglycans.

Concentrations in other organs are of the same order as in the serum. The lowest concentration occurs in the brain; practically no aprotinin passes into the cerebrospinal fluid.

Only very limited amounts of aprotinin penetrate the placental barrier. The placenta is probably not absolutely impermeable to aprotinin, but permeation appears to take a very slow course.

No studies are available on the passage of aprotinin into the mother's milk. However, since aprotinin is not bioavailable after oral administration, any drug contained in the milk would have no effect on the baby.

Metabolism, elimination and excretion

The aprotinin molecule is metabolised to shorter peptides or amino acids by lysosomal activity in the kidney. In man, urinary excretion of active aprotinin accounts for less than 5 % of the dose. After receiving injections of ^{131}I-aprotinin, healthy volunteers excreted within 48 hours 25-40% of the labelled substance as metabolites in the urine. These metabolites lacked enzyme-inhibitory activity.

No pharmacokinetic studies are available in patients with terminal renal insufficiency. Studies in patients with renal impairment revealed no clinically significant pharmacokinetic alterations or obvious side effects. A special dose adjustment is not warranted.

PRECLINICAL SAFETY DATA

Acute toxicity:

Intravenous LD50 values obtained were about 2.5-6.5 million in mice, 2.5-5 million in rats, greater than 1.36 million in dogs and 500,000 KIU/kg in rabbits.

In a study designed to approximate the anticipated conditions of human use, dogs received single intravenous infusions ranging from 340,000 KIU/kg/day over 4 hours to 1,360,000 KIU/kg over 8 hours. The doses correspond with 3 to 10 times the highest recommended doses in humans. Abnormalities observed were pseudoallergic reactions and slight to moderate hyaline transformation of the cytoplasm of renal tubular epithelial cells. The morphological renal changes, which had no accompanying glomerular alterations, were not totally reversed within a 10-day recovery period.

In rats, guinea-pigs, rabbits and dogs, high doses (> 150,000 KIU/kg) injected quickly caused a blood pressure reduction of varying magnitude, which rapidly subsided.

Chronic toxicity:

Daily intraperitoneal administration of aprotinin in doses to rats ranging from 10,000 to 300,000 KIU/kg/day for 13 weeks caused reduced body weight gain in the high dose animals. At necropsy the relative weights of kidneys were found to be increased. In the renal tubules hyaline droplets and hyaline casts were observed by means of histopathological methods, in particular in the two highest dose groups (150,000 and 300,000 KIU/kg). None of the tubular changes were considered permanent and there were no glomerular alterations seen.

In another rat study after a 35-day recovery period all pathological findings in clinical chemistry as well as macroscopic and microscopic kidney changes were no longer evident, with the exception that the relative kidney weights in the high dose males and females remained elevated. It was concluded that all functional and morphological effects on the renal tubules were generally reversible within 35 days after termination of treatment.

In dogs, numerous parenteral studies with doses ranging from 5,000 to 500,000 KIU/kg/day were conducted using the intravenous or the intraperitoneal route, for periods of up to 16 weeks. The most important toxicological target in the dog as in the rat studies was the tubular epithelium of the kidneys. The reversibility of all renal (morphological and functional) effects was demonstrated by special studies including recovery groups.

Reproduction toxicity:

In rat intravenous studies, daily doses of up to 80,000 KIU/kg produced no maternal toxicity, embryotoxicity, or fetotoxicity. Daily doses of up to 100,000 KIU/kg did not interfere with the growth and development of the young, and doses of 200,000 KIU/kg/day were not teratogenic. In rabbits, daily intravenous doses of 100,000 KIU/kg produced no evidence of maternal toxicity, embryotoxicity, fetotoxicity, or teratogenicity.

Mutagenic Potential

Aprotinin gave a negative mutagenic response in the Salmonella/microsome and B.subtilis DNA damage system.

PHARMACEUTICAL PARTICULARS

List of excipients
Sodium chloride, sodium hydroxide and hydrochloric acid.

Incompatibilities

In principle, Trasylol must be regarded as being incompatible with other drugs. Administration of Trasylol in mixed infusions must be avoided.

However, the drug product is compatible with glucose 20 % solution, hydroxyethyl starch solution and Ringer lactate solution.

Special Precautions for Storage
Do not store above 25 ° C.

Trasylol must not be used after the expiry date

Keep drugs out of reach of children.

Presentation
Glass infusion bottles.
Each 50 mL bottle contains 500,000 KIU.

Instructions for use/handling

Parenteral drug products should be inspected visually for particulate matter and colour change prior to administration. Any residual solution should not be kept for later use.

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