

## DATASHEET

### TRASYLOL® *aprotinin*

#### General information

##### ***Qualitative and Quantitative Composition***

1 vial of 50 mL/100 mL/200 mL contains aprotinin concentrated solution, corresponding to 500,000 KIU (Kallikrein Inhibitor Units) /1,000,000 KIU/2,000,000 KIU in sterile isotonic sodium chloride solution.

500,000 KIU (approx. 70 mg aprotinin) corresponds to 277.8 Eur.Ph.Units  
1,000,000 KIU (approx. 140 mg aprotinin) corresponds to 555.6 Eur.Ph.Units  
2,000,000 KIU (approx. 280 mg aprotinin) corresponds to 1111.1 Eur.Ph.Units

##### ***Pharmaceutical Form***

TRASYLOL is a colourless 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, colourless, sterile isotonic solution for intravenous administration. Each millilitre 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.

#### Clinical Particulars

##### ***Indications***

TRASYLOL is used prophylactically to reduce perioperative blood loss and to reduce the need for blood transfusion in adult patients undergoing cardiopulmonary bypass in the course of isolated coronary artery bypass graft surgery, where the risk of bleeding is high (impaired haemostasis, e.g. presence of aspirin), or where transfusion is unavailable or unacceptable.

##### ***Posology and Method of Administration***

##### **Recommended usual dose:**

The following dosage 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. Before administration of TRASYLOL test dose, patients should be intubated and facilities for rapid cannulation should be available in order to place a patient on extracorporeal circulation if required. After the uneventful administration of the 1 mL test

dose, the therapeutic dose may be given. A H<sub>1</sub>-antagonist and a H<sub>2</sub>-antagonist may be administered 15 minutes prior to the test dose of TRASYLOL. In any case standard emergency treatments for anaphylactic and allergic reactions should be readily available (see "Special Warnings and Precautions for Use").

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

### **Method of Administration**

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

TRASYLOL 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 TRASYLOL 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 a dose adjustment is not necessary for patients with decreased renal function.

#### Paediatric 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.

### **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 TRASYLOL is contraindicated in these patients.

In case no aprotinin specific IgG antibody test is possible prior to treatment, administration of TRASYLOL to patients with a known or suspected previous exposure during the last 12 months is contraindicated. For patients with known or suspected history of exposure to aprotinin greater than 12 months previously (see "Special Warnings and Precautions for Use").

Aprotinin may also be a component of some fibrin sealant products and the use of these products should be included in the patient history.

### ***Special Warnings and Precautions for Use***

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.

Hypersensitivity reactions often manifest as anaphylactic/anaphylactoid reactions with hypotension the most frequent 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 a severe hypersensitivity/anaphylactic reactions.

Before initiating treatment with TRASYLOL, the recommendation below should be followed to manage a potential hypersensitivity or anaphylactic reaction:

- 1) have standard emergency treatments or hypersensitivity or anaphylactic reactions readily available in the operating room (e.g. epinephrine (adrenaline), 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 cannulation and initiation of cardiopulmonary bypass are present
- 3) delay the addition of TRASYLOL into pump prime solution until after the loading dose has been safely administered.

TRASYLOL should not be used through pregnancy unless clearly necessary and if the potential benefit justifies the potential risk (see "Pregnancy and Lactation").

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 also "Contraindications" and "Undesirable effects"). 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. In any case standard emergency treatments for allergic/anaphylactic reactions should be readily available.

An analysis of all spontaneous reports from the Bayer Global database covering a period from 1985 to March 2006 revealed that of 291 possibly associated spontaneous cases of hypersensitivity (fatal: n=52 and non-fatal: n=239), 47% (138/291) of hypersensitivity cases had documented previous exposure to TRASYLOL. Of the 138 cases with documented previous exposure, 110 had information on the time of the previous exposure. Ninety-nine of the 110 cases had previous exposure within the prior 12 months.

Test dose: All patients treated with aprotinin should first receive a test dose to assess the potential for allergic reactions (see also section “Posology and Method of Administration”). Before administration of the TRASYLOL 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.

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 Posology and Method of Administration. An H<sub>1</sub>-antagonist (e.g. clemastine) and an H<sub>2</sub>-antagonist (e.g. cimetidine) may be administered 15 minutes prior to the test dose of TRASYLOL. However, even after the uneventful administration of the initial 1 mL dose, the therapeutic dose may cause an anaphylactic reaction. If this happens, the infusion of TRASYLOL should immediately be stopped, and the standard emergency treatment for anaphylaxis be given.

Renal Effects: Results from recent observational studies indicate that renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. An analysis of all pooled placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) has found elevations of serum creatinine values >0.5 mg/dL above baseline in patients with aprotinin therapy (see “Pharmacodynamic Properties”).

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 full-dose TRASYLOL group compared with 6.6 % (129/1957) in the placebo group, with an odds ratio of 1.41 (1.12-1.79). In the majority of instances, post-operative renal dysfunction was not severe and 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 (1.1 % vs 0.8 %) in the full-dose aprotinin.

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). TRASYLOL administration increases the risk of renal dysfunction and may increase the need for dialysis in the perioperative period.

An increase in renal failure and mortality compared to age-matched historical controls has been reported for TRASYLOL-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 maintained (see also additional note below).

#### **Additional note on use with extracorporeal circulation**

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

1) 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.

2) 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 TRASYLOL 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 TRASYLOL.

In TRASYLOL treated patients the neutralisation 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.

#### *Laboratory Monitoring of Anticoagulation during Cardiopulmonary Bypass*

Activated Clotting Time (ACT) - An ACT is not a standardised 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.

Activated Clotting Time (ACT) should be used to monitor anticoagulation.

Significant elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (celite ACT) are expected in patients treated with TRASYLOL during surgery, and in the hours after surgery due to circulating concentrations of TRASYLOL, which are known to inhibit activation of the intrinsic clotting system by contact with a foreign material (eg. celite), a method used in these tests. These increases may lead to an overestimation of the degree of anticoagulation, thereby leading to inadequate anticoagulation which may be associated with an increased risk of graft closure.

The PTT alone should not be used to monitor adequate anticoagulation with heparin in patients receiving TRASYLOL.

#### **Mortality**

An association between TRASYLOL use and increased mortality has been reported in some non-randomised observational studies (e.g. Mangano 2007, Schneeweiss 2008, Olenchock 2008, Shaw 2008)<sup>1,2,3,4,5,6</sup> while other non-randomised studies have not reported such an association (e.g. Karkouti 2006, Mangano 2006, Coleman 2007, Pagano 2008, Ngaage 2008, Karkouti, 2009)<sup>7,8,9,10,11,12</sup>. In these studies, TRASYLOL was usually administered to patients who had more risk factors for increased mortality

before surgery than patients in the other treatment groups. Most of these studies did not adequately account for the baseline differences in risk factors and the influence of these risk factors on the results is not known. Therefore interpretation of these observational studies is limited and an association between TRASYLOL use and increased mortality can neither be established nor refuted. Thus, TRASYLOL should only be used as authorised in isolated CABG surgery, after careful consideration of the potential risks and benefits.

A publication by Fergusson et al 2008<sup>13,14</sup> analysed data from a randomised controlled trial, Blood Conservation Using Antifibrinolytics in a Randomised Trial (BART), reported a higher mortality trend in patients treated with TRASYLOL compared to those treated with tranexamic acid or aminocaproic acid. However, the BART study was not adequately powered for the secondary endpoint of all-cause mortality, and thus, given the small number of deaths, the mortality results reported by Fergusson et al 2008<sup>13,14</sup> could be due to statistical chance<sup>15</sup>. Also, further analysis of the data<sup>16</sup> has revealed that the PTT was significantly longer in the TRASYLOL treatment group than in the comparator groups. Less heparin was used in the TRASYLOL arm, but the reasons for this are unclear. Therefore, the available BART data on mortality do not establish nor refute association between TRASYLOL use and increased mortality.

#### ***Interaction with Other Medicaments 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).

#### ***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 TRASYLOL. Aprotinin should not be used through pregnancy unless clearly necessary and 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 foetus has to be taken into account for a risk/benefit evaluation.

##### **Lactation:**

It is not known whether aprotinin is excreted in human milk. However, since aprotinin is not bioavailable after oral administration, any drug contained in the milk would have no effect on the baby.

#### ***Effect on Ability to Drive and Use Machines***

Not applicable

#### ***Undesirable Effects***

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.

<b>Clinical Description</b>	<b>Common</b> ≥1% to <10%	<b>Uncommon</b> ≥0.1% to <1%	<b>Rare</b> ≥0.01% to <0.1%	<b>Very Rare</b> <0.01%
<b>General Disorders or Administration Site Conditions</b>				
Infusion site reactions				Injection and infusion site reactions Infusion site (thrombo-)phlebitis
<b>Cardiac Disorders</b>				
Myocardial disorders		Myocardial ischemia Coronary occlusion/ thrombosis Myocardial infarction		
Pericardial effusion		Pericardial effusion		
<b>Vascular Disorders</b>				
Embolism and thrombosis		Thrombosis	Arterial thrombosis (and its organ-specific manifestations that might occur in vital organs such as kidney, lung or brain)	<b><i>Pulmonary embolism</i></b>
<b>Blood and Lymphatic System Disorders</b>				
Changes in coagulation				<b><i>Disseminated intravascular coagulation Coagulopathy</i></b>
<b>Immune System Disorders</b>				
Acute hypersensitivity reactions			Allergic reaction Anaphylactic / anaphylactoid reaction	<b><i>Anaphylactic shock (potentially life threatening)</i></b>
<b>Renal and Urinary Disorders</b>				
Renal impairment		Oliguria, acute renal failure, renal tubular necrosis		

### **Allergic/anaphylactic reactions**

Allergic/anaphylactic reactions are rare in patients with no prior exposure to aprotinin. In cases 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 rare cases, fatal outcome.

The symptoms of allergic/anaphylactic reactions may extend from:

Cardiovascular system	hypotension
Digestive system	Nausea
Respiratory system	Asthma (bronchospasm)
Skin and appendages	Pruritus, rash, urticaria

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

### **Cardiovascular system:**

In the pooled analysis of placebo-controlled clinical studies with patients undergoing CABG surgery, 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 influenced by two centres. Sub-analyses 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 (Special Warnings and 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 infarction or of death in this study.

### **Mortality**

An association between TRASYLOL use and increase mortality has been reported in some non-randomised observational studies while other non-randomised studies have not reported such an association (see "Special Warnings and Precautions for Use").

### **Non-Bayer Randomised Controlled Clinical Trial**

A publication by Fergusson et al 2008<sup>13,14</sup> analysed data from a randomised controlled trial, Blood Conservation Using Antifibrinolytics in a Randomised Trial (BART), reported a high mortality trend in patients treated with TRASYLOL compared to those treated with tranexamic acid or aminocaproic acid. However, the BART study was not adequately powered for the secondary endpoint of all-cause mortality, and thus, given the small number of deaths, the mortality results reported by Fergusson et al 2008<sup>13,14</sup> could be

due to statistical chance<sup>15</sup>. Therefore, the available BART data on mortality do not establish nor refute association between TRASYLOL use and increased mortality.

### **Overdose**

Symptoms of overdosage or intoxication are not known. There is no specific antidote.

### **Pharmacological Properties**

#### ***Pharmacodynamic Properties***

Aprotinin is a broad spectrum proteinase 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 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-inflammatory 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.

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 full-dose TRASYLOL group compared with 6.6 % (129/1957) in the placebo group, with an odds ratio of 1.41 (1.12-1.79). In the majority of instances, post-operative renal dysfunction was not severe and reversible; the incidence of serum creatinine elevations >2.0 mg/dL above baseline was similar (1.1 % vs 0.8 %) in both the full-dose TRASYLOL and placebo group, with an odds ratio of 1.16 (0.73-1.85) (see "Special Warnings and Precautions for Use").

## ***Pharmacokinetic Properties***

### **Absorption, Distribution & Bioavailability:**

After intravenous injection, rapid distribution of aprotinin occurs into the total extra-cellular space, leading to an initial decrease in plasma aprotinin concentration with a half-life of 0.3-0.7 hours. 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 intra-operative plasma concentrations were 175-281 KIU/mL in patients treated with TRASYLOL 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 as continuous intravenous infusion. Average steady state intra-operative 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 antifibrinolytic activity was found unbound in the protein-free layer whereas 80% were bound 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 in cartilaginous tissue. Accumulation in the kidneys is due to binding to the brush border of the epithelial cells of the proximal tubules and to accumulation 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 similar to the concentrations 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 be very slow.

No studies are available on the passage of aprotinin into the mother's milk. However, since aprotinin is not bio-available 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 <sup>131</sup>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 LD<sub>50</sub> 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 after a 10-day recovery period.

An injection of high doses (> 150,000 KIU/kg) in rats, guinea-pigs, rabbits and dogs caused a rapid reduction of blood pressure of varying magnitude. This rapidly returned to normal.

### ***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 without any impairment of renal function parameters. At necropsy there was an increase in the relative weights of the kidneys. In the renal tubules hyaline droplets and hyaline casts were observed particularly 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 were no longer evident. This included macroscopic and microscopic kidney changes 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 for periods of up to 16 weeks with doses ranging from 5,000 to 500,000 KIU/kg/day were conducted using the intravenous or the intraperitoneal route. 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 these studies.

***Reproduction Toxicology:***

In rat intravenous studies, daily doses of up to 80,000 KIU/kg produced no maternal toxicity, embryotoxicity, or foetotoxicity. 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, foetotoxicity, or teratogenicity.

***Mutagenicity:***

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

**Pharmaceutical Particulars*****List of Excipients:***

Aprotinin concentrated solution, sodium chloride

***Incompatibilities:***

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

However, TRASYLOL is compatible with glucose 20 % solution, hydroxyethyl starch solution and Ringer lactate solution.

***Shelf-life:***

36 months from date of manufacture.

***Special Precautions for Storage:***

Do not store above 25 °C.

***Nature and Contents of Container:***

Glass infusion bottles, colourless, glass type 2:

Vials of 500,000 KIU/ 50 mL

Vials of 1,000,000 KIU/100 mL

Vials of 2,000,000 KIU/200 mL

Not all pack sizes maybe marketed

***Instruction 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.

**Medicine Classification:**

Prescription Medicine

**Name and Address:**

Bayer New Zealand Limited  
3 Argus Place  
Hillcrest, North Shore AUCKLAND 0627  
New Zealand

Freephone 0800 233 988

**Date of Preparation:**

12 January 2012

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<sup>2</sup> Olenchock S, Lee P, Yehoshua T, Murphy S, Symes J, Tolis G. Impact of Aprotinin on Adverse Clinical Outcomes and Mortality up to 12 Years in a Registry of 3,337 Patients. *Ann Thorac Surg*. 2008;86:560-7.

<sup>3</sup> Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med*. 2008;358(8):771-83.

<sup>4</sup> Schneeweiss S, Seeger JD, Landon J, Walker AM. Supplementary appendix to: Aprotinin during coronary-artery bypass grafting and risk of death. Available from <http://content.nejm.org/cgi/content/full/358/8/771/DC1>, accessed September 8, 2009. *N Engl J Med*. 2008;358(8):771-83.

<sup>5</sup> Shaw AD, Stafford-Smith M, White WD, Phillips-Bute B, Swaminathan M, Milano C, et al. The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med*. 2008;358(8):784-93.

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<sup>8</sup> Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 2006;46(3):327-38.

<sup>9</sup> Karkouti K, Wijesundera DN, Yau TM, McCluskey SA, Tait G, Beattie WS. The Risk-Benefit Profile of Aprotinin Versus Tranexamic Acid in Cardiac Surgery. *Anesth Analg*. 2009.

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