Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trasylol 10,000 KIU/ml, solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains: Aprotinin 10,000 KIU (Kallikrein Inhibitor Units)

For a full list ofexcipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection/infusion
The solution is clear and colourless

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aprotinin is indicated for prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).

Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available (see section 4.4 and 5.1).

4.2 Posology and method of administration

Posology

An appropriate aprotinin-specific IgG antibody test may be considered if available before administration of aprotinin (see section 4.3).

Adult:
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 H1-antagonist and a H2-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 section 4.4).

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.

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

Paediatric population
The safety and efficacy in children below 18 years of age have not been established.

Renal impairment

Available clinical experience suggests that patients with decreased renal function do not require special dose adjustment.

Hepatic impairment
No data are available on dosage recommendations for patients with hepatic dysfunction.

Elderly
Reported clinical experience has not identified differences in responses in elderly patients.

Method of administration

Aprotinin should be infused using a central venous catheter. The same lumen should not be used for the administration of any other medicinal product.
When using a multi-lumen central catheter a separate catheter is not required.

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.

Aprotinin should be prescribed by specialists with experience in cardiopulmonary bypass graft surgery.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

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 including in fibrin sealant products during the last 12 months is contraindicated.

4.4 Special warnings and precautions for use

Aprotinin should not be used when CABG surgery is combined with another cardiovascular surgery because the benefit risk balance of aprotinin in other cardiovascular procedures has not been established.

*Laboratory monitoring of anticoagulation during cardiopulmonary bypass*Aprotinin is not a heparin-sparing agent and it is important that adequate anticoagulation with heparin be maintained during aprotinin-therapy.

The partial thromboplastin time (PTT) and activated partial thromboplastin time (APTT) are similar and become immeasurable with high doses of heparin. Therefore, APTT and PTT should not be used to monitor anticoagulation with heparin in patients undergoing cardiopulmonary bypass graft surgery.
In patients undergoing cardiopulmonary bypass graft surgery with aprotinin therapy, one of the following methods is recommended to maintain adequate anticoagulation:

1. Individualized heparin and protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications in cardiac surgery with cardiopulmonary bypass (CPB). Individualized heparin management or titration is based on computer-based heparin dosing systems, anti-Xa measurements or blood heparin measurements in addition to the Activated Clotting Time (ACT). Anti-Xa measurement and blood heparin measurements are unaffected by aprotinin and should be carried out following test-manufacturer's notices.

2. In the absence of individual heparin dosing tools, it is recommended that ACT tests are performed at regular intervals based on institutional protocols, and heparin doses have to be given accordingly. The required target ACT is dependent on the type of activator and equipment used. Elevations of kaolin and celite ACT are expected in aprotinin-treated patients during surgery, and in the hours after surgery. In patients undergoing cardiopulmonary bypass with aprotinin therapy, a minimal celite ACT of 750 seconds or kaolin ACT of 480 seconds is recommended to maintain anticoagulation, independent of the effects of haemodilution and hypothermia. ACT tests using a mixture of activators should be carried out following test-manufacturer's notices.

Protamine management

As the protamine test is unaffected by aprotinin in aprotinin treated patients the neutralisation of heparin by protamine after discontinuation of cardiopulmonary bypass should be carried out following test-manufacturer's notices.

Graft Conservation

Blood drawn from the aprotinin central infusion line should not be used for graft preservation.

Re-exposure to aprotinin

Administration of aprotinin, especially to patients who have received aprotinin (including aprotinin containing fibrin sealants) in the past requires a careful risk/benefit assessment because an allergic reaction may occur (see sections 4.3 and 4.8). 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.

Assessment of potential for allergic reactions

All patients treated with aprotinin should first receive a test dose to assess the potential for allergic reactions (see section 4.2). The test dose of aprotinin should only be administered when facilities and equipment for handling acute anaphylactic reactions are available on-site.

Renal impairment

Results from prior 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 section 5.1).

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.

Careful consideration of the balance of risks and benefits is therefore advised before administration of aprotinin to patients with pre-existing impaired renal function or those with risk factors (such as concomitant treatment with aminoglycosides).

Mortality

Information on mortality from randomized clinical trials is provided in section 5.1.

An association between aprotinin use and increased mortality has been reported in some non-randomized observational studies (eg, Mangano 2007, Schneeweiss 2008, Olenchock 2008, Shaw 2008) while other non-randomized studies have not reported such an association (eg, Karkouti 2006, Mangano 2006, Coleman 2007, Pagano 2008, Ngaage 2008, Karkouti, 2009). In these studies, aprotinin was usually administered to patients who had more risk factors for increased mortality before surgery than patients in the other treatment groups.

Most of the studies did not adequately account for these 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 aprotinin use and increased mortality can neither be established nor refuted. Thus, aprotinin should only be used as authorized in isolated CABG surgery, after careful consideration of the potential risks and benefits.

A publication by Fergusson et al in 2008 analyzed data from a randomized controlled trial, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), and reported a higher mortality rate in aprotinin-treated patients compared to those treated with tranexamic acid or aminocaproic acid.
However, due to several methodological deficiencies no firm conclusion on cardiovascular risks can be made on the BART study results.

4.5 Interaction with other medicinal products and other forms of interaction

Aprotinin has a dose-dependent inhibitory effect on the action of thrombolytic agents, e.g. streptokinase, urokinase, alteplase (r-tPA). Special attention to coagulation should be paid in patients receiving active thrombolytic agents known to be aprotinin targets.

Renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. Drugs with a potent nephrotoxic profile (such as aminoglycosides and renin-angiotensin-aldosterone system inhibitors) are a risk factor for renal dysfunction. Special attention to kidney protection should be paid when exposing patients to both aprotinin and other drugs that could trigger a kidney dysfunction.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Animal studies did not provide any evidence of teratogenic or other embryotoxic effects of Trasylol.
Trasylol 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 foetus has to be taken into account for a risk/benefit evaluation.

Breastfeeding
It is unknown whether aprotinin is excreted in human milk. However, since aprotinin is not bioavailable after oral administration, any drug contained in the milk is not expected to have a systemic effect on the breast-feed child.

Fertility
There are no adequate and well-controlled studies addressing fertility in men or women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
The safety of Trasylol has been evaluated in more than 45 phase II and phase III studies including more than 3800 patients exposed to aprotinin. In total, about 11% of aprotinin-treated patients experienced adverse reactions. The most serious adverse reaction was myocardial infarction. The safety of aprotinin has been monitored in the NAPaR between February 2016 and November 2020. Of the 6682 entered patients, the rate of adverse drug reaction was 1.1%. The adverse reactions should be interpreted within the surgical setting.

Tabulated summary of adverse reactions
Adverse drug reactions 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) and based on the NAPaR are listed in the table below:

Not known: cannot be estimated from the available data

MedDRA Standard System organ class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Very Rare** < 1/10,000
Immune system disorders		Allergic reactionAnaphylactic / anaphylactoid reaction		***Anaphylactic shock (potentially life threatening)***
Blood and lymphatic system				***Disseminated intravascular coagulation***

disorders				***Coagulopathy***
Cardiac disorders		Myocardial ischaemia Coronary occlusion/ thrombosis Myocardial infarction Pericardial effusion		
Vascular disorders		Thrombosis, embolic stroke	Arterial thrombosis (and its organ specific manifestations that might occur in vital organs such as kidney, lung or brain), Pulmonary embolism	
Renal and urinary disorders		Oliguria, acute kidney failure, renal tubular necrosis		
General disorders and administration site conditions				Injection and infusion site reactions Infusion site (thrombo-) phlebitis
Investigations	Blood creatinine increased			

- Adverse Drug Reactions derived from post-marketing reports are printed in ***bold italic***

Description of selected adverse reactions

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, 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.

Mortality
For the risk of mortality associated with the use of aprotinin see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Toxicity: There is limited experience of overdose

Symptoms: Nausea, vomiting, diarrhea, muscle pain, unstable blood pressure

Treatment: There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, proteinase inhibitors, ATC code: B02AB01

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.
Aprotinin is a basic polypeptide with a molecular weight of about 6,500. It is made up of a chain of 58 amino acids. The isoelectric point of the substance is at about pH 10. One KIU (kallikrein inhibitor unit) corresponds to 0.14 micrograms of crystalline substance. Trasylol is a standardized biological product.

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 aprotinin 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 aprotinin and placebo group, with an odds ratio of 1.16 (0.73 - 1.85) (see section 4.4).

The in-hospital mortality in Bayer's pool of randomized, clinical trials is summarized in the table below:

In-hospital Mortality in Bayer's pool of Randomized Clinical Trials (Population: All Global CABG Patients Valid for Safety)					
Population	**Full-Dose Aprotinin**		**Placebo**		**Odds Ratio (95% CI)**
	n/N	**%**	**n/N**	**%**	
All CABG	65/2249	2.9	55/2164	2.5	1.09 (0.78, 1.52)
Primary CABG	36/1819	2.0	39/1785	2.2	0.92 (0.62, 1.38)
Repeat CABG	22/276	8.0	13/255	5.1	1.47 (0.75, 2.87)

The Nordic Aprotinin Patient Registry (NAPaR), a multicenter non-interventional active surveillance post-authorisation study, aimed, among other outcomes, to measure the incidence of safety outcomes. A subgroup of 1,384 patients undergoing an isolated CABG (iCABG) was treated with aprotinin. In-hospital mortality was 1.3% (95% CI: 0.73%, 1.96%). Incidences of myocardial infarction and thromboembolic events (TEEs) were 0.9% (95% CI: 0.39%, 1.39%) and 2.5% (95% CI: 1.63%, 3.28%), respectively. Renal dysfunction (postoperative rise in creatinine level >0.5 mg/dL) and renal failure (postoperative rise in serum creatinine level >2.0 mg/dL) were observed with incidences of 2.7% (95% CI: 1.82%, 3.55%) and 0.15% (95% CI: 0.02%, 0.54%), respectively. Within 24 hours following the procedure 1.3% (95% CI: 0.73%, 1.96%) of patients underwent re-exploration for bleeding. When comparing with a historical control from literature, the findings from the NAPaR were essentially in accordance with the known safety profile of aprotinin in the approved indication.

5.2 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.

The mean steady-state plasma concentration in the treatment of aprotinin in cardiac surgery is 175-280 KIU/ml (at full dose). In the alternative dosage recommendation (half dose), the corresponding plasma concentration is 110-164 KIU/ml. Plasma protein binding is about 80% and the volume of distribution is about 20 liters.

The placenta is probably not absolutely impermeable to aprotinin, but permeation appears to take a very slow course.

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.

Total clearance is 40 ml/min.

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.

5.3 Preclinical safety data

Acute toxicity

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.

Reproduction toxicity

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.

Mutagenic potential

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

This product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in original container to protect from light.

6.5 Nature and contents of container

50 ml solution for injection / infusion (Type I glass) with rubber stopper (bromobutyl)

6.6 Special precautions for disposal and other 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.

Trasylol is compatible with glucose 20% solution, hydroxyethyl starch solution or Ringer lactate solution. Chemical and physical stability has been demonstrated for diluted solution for up to 6 hours at 25 °C. From a microbiological point of view, the product should be used immediately unless the preparation has been carried out under controlled and validated aseptic conditions. If the product is not used immediately, storage during use and condition prior to use is the responsibility of the user

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Nordic Group B.V.
Siriusdreef 22
Hoofddorp
2132 WT
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2252/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th March 2018
Date of last renewal: 6th February 2023

10 DATE OF REVISION OF THE TEXT

June 2024