

## **Annex III**

### **Summary of Product Characteristics and Package Leaflet**

**SUMMARY OF PRODUCT CHARACTERISTICS  
AND PACKAGE LEAFLET**

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

<Aprotinin-containing medicinal product>  
[See Annex I - To be completed nationally]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

## 3. PHARMACEUTICAL FORM

[To be completed nationally]

## 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 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 H<sub>1</sub>-antagonist and a H<sub>2</sub>-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.

### **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. Elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (Celite ACT) are expected in aprotinin-treated patients during surgery, and in the hours after surgery. **Therefore, the partial thromboplastin time (PTT) should not be used to maintain adequate anticoagulation with heparin. In patients undergoing cardiopulmonary bypass with aprotinin therapy, one of three methods is recommended to maintain adequate anticoagulation: Activated Clotting Time (ACT), Fixed Heparin Dosing, or Heparin Titration (see below). If activated clotting time (ACT) is used to maintain adequate anticoagulation, 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.**

#### *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:

- 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.

- 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.

- 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 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: aprotinin is not a heparin-sparing agent.

#### 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 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 section 5.1). 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).

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. Adequate anticoagulation with heparin must be assured (see also above).

#### 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, Olenchok 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 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).

Renal dysfunction could be triggered by aprotinin, particularly in patients with pre-existing renal dysfunction. Aminoglycosides are a risk factor for renal 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 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 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 aprotinin has been evaluated in more than forty five 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 adverse reactions should be interpreted within the surgical setting.

##### *Tabulated summary of adverse reactions*

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 in the table below:

Frequencies are defined as:

Common:  $\geq 1/100$  to  $< 1/10$

Uncommon:  $\geq 1/1,000$  to  $< 1/100$

Rare:  $\geq 1/10,000$  to  $< 1/1,000$

Very rare:  $< 1/10,000$

Not known: cannot be estimated from the available data

MedDRA Standard System organ class	Common	Uncommon	Rare	Very Rare
Immune system disorders			Allergic reaction Anaphylactic / anaphylactoid reaction	<b>Anaphylactic shock (potentially life threatening)</b>
Blood and lymphatic system disorders				<b>Disseminated intravascular coagulation Coagulopathy</b>
Cardiac disorders		Myocardial ischaemia Coronary occlusion/ thrombosis Myocardial infarction Pericardial effusion		
Vascular disorders		Thrombosis	Arterial thrombosis (and its organ specific manifestations that might occur in vital organs such as kidney, lung or brain)	<b>Pulmonary embolism</b>
Renal and urinary disorders		Oliguria, acute renal failure, renal tubular necrosis		
General disorders or administration site conditions				Injection and infusion site reactions Infusion site (thrombo-) phlebitis

- ADRs 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/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.

## Mortality

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

## 4.9 Overdose

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.

Data from a 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 a pool of randomized, clinical trials is summarized in the table below:

<b>In-hospital Mortality in a pool of Randomized Clinical Trials (Population: All Global CABG Patients Valid for Safety)</b>					
<b>Population</b>	<b>Full-Dose Aprotinin</b>		<b>Placebo</b>		<b>Odds Ratio (95% CI)</b>
	<b>n/N</b>	<b>%</b>	<b>n/N</b>	<b>%</b>	
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)

### 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 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 <sup>131</sup>I-protinin 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.

## **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 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

[To be completed nationally]

### **6.2 Incompatibilities**

[To be completed nationally]

### **6.3 Shelf life**

[To be completed nationally]

### **6.4 Special precautions for storage**

[To be completed nationally]

### **6.5 Nature and contents of container**

[To be completed nationally]

### **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.

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

## **7. MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and address}  
<{tel}>  
<{fax}>  
<{e-mail}>

**8. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

**10. DATE OF REVISION OF THE TEXT**

[To be completed nationally]

**PACKAGE LEAFLET**

## Package leaflet: Information for the patient

<Aprotinin-containing medicinal product>

[See Annex I - To be completed nationally]

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor/surgeon giving you <Aprotinin-containing medicinal product>.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

### What is in this leaflet

1. What <Aprotinin-containing medicinal product> is and what it is used for
2. What you need to know before you are given <Aprotinin-containing medicinal product>
3. How to use <Aprotinin-containing medicinal product>
4. Possible side effects
5. How to store <Aprotinin-containing medicinal product>
6. Contents of the pack and other information

### 1. What <Aprotinin-containing medicinal product> is and what it is used for

<Aprotinin-containing medicinal product> belongs to a group of medicines called anti-fibrinolytics, i.e. medicines to prevent blood loss.

<Aprotinin-containing medicinal product> can help to reduce the amount of blood loss you have during and after heart surgery. It is also used to reduce the need for a blood transfusion during and after heart surgery. Your doctor/surgeon has decided that you would benefit from <Aprotinin-containing medicinal product> treatment because you are at increased risk of major blood loss since you will undergo a heart bypass operation using a circulation outside your body (heart-lung machine).

Your doctor will administer aprotinin after careful consideration of the benefits and risks, and the availability of alternative treatments.

### 2. What you need to know before you are given <Aprotinin-containing medicinal product>

**You must not be given <Aprotinin-containing medicinal product>**

- if you are **allergic to <Aprotinin-containing medicinal product>** or any of the other ingredients of this medicine (listed in section 6).
- if a **positive aprotinin-specific IgG antibody** test is available, showing an increased risk of an allergic reaction to <Aprotinin-containing medicinal product>.
- if no aprotinin specific IgG antibody test is possible prior to treatment and you have received or you suspect that you have received <Aprotinin-containing medicinal product> in the last 12 months.

### Warnings and precautions

**Talk to your doctor before receiving <Aprotinin-containing medicinal product>.**

**Tell your doctor if any of these apply to you**, to help him or her decide if <Aprotinin-containing medicinal product> is suitable for you:

- **Your kidneys do not work properly.** If you have kidney problems <Aprotinin-containing medicinal product> should only be used if your doctor/surgeon feels it will be of benefit.
- **You have or suspect you have received aprotinin or aprotinin containing fibrin sealants in the last 12 months.**

If any of these apply to you, your doctor will decide whether <Aprotinin-containing medicinal product> is suitable for you or not.

<Aprotinin-containing medicinal product> will only be given if your doctor has done **blood tests before** to check you are suitable (e.g. an appropriate aprotinin-specific IgG antibody test), otherwise other medicines may be a better option for you.

**You will be monitored carefully for any allergic reaction to the medicine** and your doctor/surgeon will treat any symptoms you may experience. Standard emergency treatment for severe allergic reactions should be readily available during treatment with <Aprotinin-containing medicinal product>.

### **Children and adolescents**

The safety and efficacy of <Aprotinin-containing medicinal product> in children below the age of 18 years have not been established.

### **Other medicines and <Aprotinin-containing medicinal product>**

Tell your doctor if you are taking, have recently taken or might take any other medicines.

You should specifically tell your doctor if you take:

- medicines used to dissolve blood clots, such as streptokinase, urokinase, alteplase (r-tPA)
- aminoglycosides (antibiotics, medicines used to treat infections)

It is recommended that your doctor/surgeon should, in addition to <Aprotinin-containing medicinal product>, administer heparin (a medicine used to prevent blood clots) before and during the operation. Your doctor will evaluate the dose of heparin based from the results from tests of your blood.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine. If you are pregnant or breast-feeding <Aprotinin-containing medicinal product> should only be used if your doctor/surgeon finds it will be of benefit. Your doctor will discuss with you the risks and benefits of using this medicine.

## **3. How to use <Aprotinin-containing medicinal product>**

For adult patients the following dose regimen is recommended:

You will receive a small amount of <Aprotinin-containing medicinal product> (1 ml) before the operation begins, to test if you are allergic to the <Aprotinin-containing medicinal product>. Medicines used to prevent the symptoms of allergy (H<sub>1</sub>-antagonist and a H<sub>2</sub>-antagonist) may be administered 15 minutes prior to the test dose of <Aprotinin-containing medicinal product>.

If there are no signs of allergy, you will be given 100-200 ml <Aprotinin-containing medicinal product> over 20 to 30 minutes, followed by 25 - 50 ml per hour (max. 5 - 10 ml/min) until the end of the operation.

In general, you will not be given more than 700 ml of <Aprotinin-containing medicinal product> at any one time.

There is no special dose recommendation for elderly patients or patients with poor kidney function

<Aprotinin-containing medicinal product> will usually be given to you lying down by slow injection or infusion (through 'a drip') through a catheter into a larger vein in your body.

### **If you are given more <Aprotinin-containing medicinal product> than the recommended dose**

There is no specific substance to counteract the effects of <Aprotinin-containing medicinal product>.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Although allergic reactions are rare in patients receiving <Aprotinin-containing medicinal product> for the first time, patients who are given <Aprotinin-containing medicinal product> more than once may have an increased chance of an allergic reaction. The symptoms of an allergic reaction may include:

- **breathing difficulties**
- **reduced blood pressure**
- **itching, rash and hives**
- **feeling sick**

If any of these occur during administration of <Aprotinin-containing medicinal product> your doctor/surgeon will stop treatment with the drug.

Other side effects are:

**Uncommon:** may affect up to 1 in 100 patients

- chest pain (*myocardial ischaemia, coronary occlusion / thrombosis*), heart attack (*myocardial infarction*)
- leakage of heart fluid into the surrounding body cavity (*pericardial effusion*)
- blood clot (*thrombosis*)
- kidney disease (*acute renal failure, renal tubular necrosis*)
- passing less urine than is normal

**Rare:** may affect up to 1 in 1,000 patients

- blood clot in blood vessels (*arteries*)
- severe allergic reaction (*anaphylactic / anaphylactoid reaction*)

**Very rare:** may affect up to 1 in 10,000 patients

- swelling on or around the location of the injected skin (injection and infusion site reactions, infusion site (*thrombo-*) *phlebitis*)
- blood clot in the lungs (*pulmonary embolism*)
- severe blood clotting disorder that results in tissue damage and bleeding (*disseminated intravascular coagulation*)
- inability of the blood to clot or coagulate normally (*coagulopathy*)
- severe allergic shock (*anaphylactic shock*), which is potentially life threatening

If you get any side effects, talk to your doctor. This includes any side effects not listed in this leaflet.

#### 5. How to store <Aprotinin-containing medicinal product>

[To be completed nationally]

#### 6. Contents of the pack and other information

**What <Aprotinin-containing medicinal product> contains**

[To be completed nationally]

**What <Aprotinin-containing medicinal product> looks like and contents of the pack**

[To be completed nationally]

**Marketing Authorisation Holder and Manufacturer**

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.**

[To be completed nationally]