Annex I

List of the invented names, pharmaceutical forms, strengths of the medicinal products, route of administration, marketing authorisation holders in the member states

Aprotinin containing medicinal products with Marketing Authorisation in the European Union

Member State (EU/EEA)	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
AT - Austria	Bayer Austria GmbH Herbststraße 6-10 A-1160 Wien Austria	Trasylol 10.000 KIE/ml - Infusionsflasche	10.000 KIU/ml	solution for infusion	intravenous use
BE-Belgium	Belgium Bayer S.A. 14, J.E. Mommaertslaan B- 1831 Diegem Belgium	Trasylol	10.000 KIU/ml	solution for infusion	intravenous use
CZ - Czech Republic	Chemical Works of Gedeon Richter Plc., HU-1103 Budapest, Gyömrői út 19-21., Hungary	Gordox	10 ku/ml	solution for injection	intravenous use
CZ - Czech Republic	Bayer Schering Pharma AG Mullerstrasse 178 13353 Berlin Germany	Trasylol 500 000 KIE	10 ku/ml	solution for infusion	intravenous use
DE - Germany	Bayer Pharma Aktiengesellschaft registered business address: Müllerstr. 178 D-13353 Berlin postal address: D-13342 Berlin	Trasynin 0,5	70.0 mg /50 ml	solution for infusion	intravenous use

DE - Germany	Bayer Pharma Aktiengesellschaft registered business address: Müllerstr. 178 D-13353 Berlin postal address: D-13342 Berlin	Trasynin 1,0	140.0 mg /100 ml	solution for infusion	intravenous use
DE - Germany	Bayer Pharma Aktiengesellschaft registered business address: Müllerstr. 78 D-13353 Berlin postal address: D-13342 Berlin	Trasynin 2,0	280.0 mg /200 ml	solution for infusion	intravenous use
DE - Germany	Bayer Vital GmbH D-51373 Leverkusen	Trasylol 0,5	70.0 mg /50 ml	solution for infusion	intravenous use
DE - Germany	Bayer Vital GmbH D-51373 Leverkusen	Trasylol 1,0	140.0 mg /100 ml	solution for infusion	intravenous use
DE - Germany	Bayer Vital GmbH D-51373 Leverkusen	Trasylol 2,0	280.0 mg /200 ml	solution for infusion	intravenous use
DK - Denmark	Bayer Schering Pharma AG, Müllerstrasse 170-178, DE-13342 Berlin, Germany	Trasylol	10.000 KIE/ml	solution for injection	intravenous use

EL - Greece	Bayer Hellas AG 18 - 20 , Sorou Str. 151 25 , Marousi - Athens	TRASYLOL	500000 KIU/50ML	solution for infusion	intravenous use
ES - Spain	QUIMICA FARMACEUTICA BAYER, S.L Av. Baix Llobregat, 3-5 08970 Sant Joan Despi Barcelona - España	TRASYLOL SOLUCIÓN PARA PERFUSIÓN INTRAVENOSA	10.000 K10.000 KIU/ml IU/ml	solution for perfusion	intravenous use
FI - Finland	Bayer HealthCare AG, 51368 Leverkusen, Germany	TRASYLOL	10 000 KIU/ml	solution for injection/infusion	intravenous use
FR - France	BAYER SANTE - 220, avenue de la recherche - 59120 LOOS	Trasylol	1 000 000 KUI/100 mL	solution for injection	intravenous use
FR - France	BAYER SANTE - 220, avenue de la recherche - 59120 LOOS	Trasylol	2 000 000 KUI/200 mL	solution for injection	intravenous use
FR - France	BAYER SANTE - 220, avenue de la recherche - 59120 LOOS	Trasylol	500 000 UIK/50 mL	solution for injection	intravenous use
HU - Hungary	Richter Gedeon Nyrt. Gyömrői út 19-21. 1103 Budapest, Hungary	Gordox	100 000 KIU/10 ml	solution for injection	intravenous use

HU - Hungary	Richter Gedeon Nyrt. Gyömrői út 19-21. 1103 Budapest, Hungary	Gordox	500 000 KIU/50 ml	solution for infusion	intravenous use
HU - Hungary	Bayer Healthcare AG Kaiser-Wilhelm-Allee, Bldg. E39 51368 Leverkusen, Germany	Trasylol	500 000 KIU/50 ml	solution for infusion	intravenous use
LU - Luxembourg	Bayer S.A. 14, J.E. Mommaertslaan B- 1831 Diegem	TRASYLOL	50.000U/50ml	solution for injection	intravenous use
LV - Latvia	Gedeon Richter Ltd. Gyomroi ut 19-21 Budapest HU-1103 Hungary	Gordox 10 000 KSV/ml šķīdums infūzijām	10 000 KIU/ml	solution for infusion	intravenous use
MT - Malta	Bayer Plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA United Kingdom trading as Bayer Plc, Pharmaceutical division	TRASYLOL	10000KIU/ML	solution for infusion	intravenous use
NL - Netherlands	Bayer B.V. Energieweg 1 3641 RT Mijdrecht The Netherlands	Trasylol 500.000, oplossing voor infusie 10.000 KIE/ml	10.000 KIU/ml	solution for infusion	intravenous use

PL - Poland	Bayer Pharma AG Berlin, D-13342 Germany	Trasylol	555,6 Ph.Eur.u. (1 000 000 KIU)	solution for infusion	intravenous use
PL - Poland	Bayer Pharma AG Berlin, D-13342 Germany	Trasylol	1111,1 Ph.Eur.u. (2 000 000 KIU)	solution for infusion	intravenous use
PL - Poland	Bayer Pharma AG Berlin, D-13342, Germany	Trasylol	277,8 j. Ph. Eur. (500 000 KIU)	solution for infusion	intravenous use
PT - Portugal	Bayer Portugal, S.A. Rua Quinta do Pinheiro 5 2794-003 Carnaxide Portugal	Trasylol	500000 U.I.C/50 ml	solution for infusion	intravenous use
PT - Portugal	Bayer Portugal, S.A. Rua Quinta do Pinheiro 5 2794-003 Carnaxide Portugal	Trasylol 1.000.000 UIC	1000000 U.I.C/100 ml	solution for infusion	intravenous use
PT - Portugal	Bayer Portugal, S.A. Rua Quinta do Pinheiro 5 2794-003 Carnaxide Portugal	Trasylol 2.000.000 UIC	2000000 U.I.C/200 ml	solution for infusion	Intravenous use
SE - Sweden	Bayer Schering Pharma AG Müllerstrasse 178 DE-133 42 Berlin Germany	Trasylol	10000 KIE/ml	solution for injection/infusion	intravenous use

SK - Slovakia	Richter Gedeon Nyrt., Budapest 10, Pf. 27., H-1475 Hungary	GORDOX	100 000 IU/10 ml	solution for injection	intravenous use
SL - Slovenia	Bayer d.o.o., Bravničarjeva 13, Ljubljana, Slovenia	TRASYLOL	10 000 KIU/ml	solution for injection and infusion	intravenous use
UK - United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury, Berkshire RG14 1JA UK	Trasylol Solution	10,000 KIU/ML	solution for injection	intravenous use
UK - United Kingdom	Nordic Pharma Limited, Abbey House, 1650 Arlington Business Park, Theale, Reading, Berkshire RG7 4SA, UK	Aprotinin 10,000 KIU/ml Injection	10,000 KIU/ml	solution for injection	intravenous use

Annex II

Scientific conclusions and grounds for lifting of the suspension and amendment of the marketing authorisations for aprotinin containing medicinal products presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of referral on antifibrinolytics **Aprotinin containing medicinal products** (see Annex I)

Antifibrinolytics (e.g. aprotinin, aminocaproic acid and tranexamic acid), are a class of haemostatic agents used to prevent excessive blood loss. Aprotinin, a naturally occurring polypeptide, is an inhibitor of proteolytic enzymes. It has a broad action on proteolytic enzymes such as plasmin, trypsin, and kallikrein. The lysine analogues epsilon aminocaproic acid (EACA, also referred as aminocaproic acid) and tranexamic acid (TXA) inhibit more specifically the conversion of plasminogen to plasmin.

In March 2010 Germany triggered an article 31 referral to assess the benefits and risks of the antifibrinolytic drugs aprotinin, EACA and TXA in all their approved indications. The marketing authorisations for aprotinin were suspended when concerns over its safety were raised in a previous review in 2007. The preliminary results of a randomised controlled clinical trial, the 'Blood conservation using antifibrinolytics: a randomised trial in a cardiac surgery population' (BART) study, had shown that although the use of aprotinin was associated with less serious bleeding than either of the comparator drugs, an increase in 30 day all-cause mortality had been observed among patients receiving aprotinin compared to patients taking other medicines. These concerns echoed those of a few published observational studies. The marketing authorisations of EACA and TXA were not affected by the initial 2007 review.

Several data sources informed the opinion of the Committee, including available data from clinical studies, published literature, spontaneous reports and other data submitted by marketing authorisation holders (MAHs) of medicinal products containing aprotinin, EACA or TXA. A CHMP scientific advisory group (SAG) meeting was held in October 2011 and its views were considered by the CHMP in the framework of this review.

Separate opinions and conclusions were issued by the CHMP for the three antifibrinolytics (aprotinin, EACA and TXA). This document presents the conclusions on aprotinin.

Aprotinin

The marketing authorisations for aprotinin were suspended following the preliminary results of the BART study in 2007, and concerns raised over some observational studies.
The final results of BART study have since become available, together with important new analysis of the study data. A comprehensive review was undertaken and the CHMP concluded that the final BART study results were seriously compromised by several newly identified major methodological deficiencies, which were considered crucial to the validity and interpretation of the results. The deficiencies included the unexplained exclusion of patients from analysis, underlying differences in baseline characteristics between the study groups which were not homogenous in spite of randomisation, and the apparent reduced level of heparinisation in the aprotinin arm which would increase the risk of thrombogenic events in this group.

Based on the final results and new evidence from re-analysis of data pointing out the deficiencies of the study that emerged after finalisation of the BART study, the CHMP is of the opinion that these data are not reliable and cannot be considered with regards to the cardiovascular risks of aprotinin. Overall, the CHMP considered that the BART study was not designed to reliably determine the risk of death associated with aprotinin in relation to EACA or TXA and the results of higher mortality initially observed in aprotinin treated patients may be due to chance. The CHMP noted that since the initial review in 2007, more data has become available, in particular the final study results, and more importantly new analysis of the BART study. These new data have now made it possible to identify the major flaws of the BART study, not identifiable before.

The CHMP noted that the findings from other randomised clinical trials and meta-analysis of randomised clinical trials (when the BART study is excluded) do not provide evidence of an association between aprotinin and perioperative mortality.

In the initial review in 2007 concerns had also been raised by the findings of three observational studies. The results of re-analysis of two of these studies did not show a statistically significant association between aprotinin treatment and myocardial infarction, and other cardiovascular endpoints; methodological questions were raised over a third observational study where a supplementary analysis also did not show a significant association between aprotinin and seven-day in-hospital mortality. New

observational studies are now available and results showed that aprotinin did not affect in-hospital mortality, with one study reporting a statistically significant mortality 'benefit' for aprotinin in high-risk cardiac surgery patients, compared with TXA. The CHMP noted the uncertainties and advised that the interpretation of all available data from observational studies is limited.
The CHMP considered that the efficacy of aprotinin has been clearly demonstrated in prospective randomised trials and meta-analysis of clinical trials which show that aprotinin reduces the incidence of massive bleeding, reduces the need for transfusion of blood products and reduces the need for re-surgery for bleeding in patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB).

Aprotinin was already indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in those patients undergoing CPB in the course of CABG who were at an increased risk for blood loss and blood transfusion. Sufficient evidence of efficacy in this patient population is available. The new data available to date however showed that the indication, and other sections of the product information, merited change, to take due account of known risks and the uncertainties associated with such risks. The product has been used outside its indication, with several trials where risks were observed conducted in a wider patient population. The CHMP considered that a clarification should be included in the wording of the indication to reflect that the product should be used in patients undergoing CPB in the course of 'isolated CABG' surgery, as efficacy and safety of aprotinin in more extensive surgery has not been sufficiently characterised. In addition, aprotinin should be used only in adult patients (data in children are not available) who are at 'high-risk' of major blood loss. There are no indications that the efficacy would vary by age or that the safety pattern of aprotinin would be different in elderly patients as compared to the overall study populations.

A review of the product information was undertaken to specify the agreed target population and update the clinical part of the product information to ensure that the information to healthcare professionals and patients is up to date. The quality review of documents templates were taken into account during this review.

The CHMP considered that overall the data provided illustrate the risks associated with inadequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure. Other notable safety concerns include the identified risk for transient renal impairment, which is a well characterised unfavourable effect of treatment with aprotinin. This is important to take into consideration when treating patients with known pre-existing impairment and in patients concomitantly treated with drugs that may affect renal function. Anaphylactic reactions are another well-known adverse effect that primarily occurs after repeated treatment. In case of repeated treatment, physicians should be aware of the risk, and manage their patients adequately. The CHMP considered that all of these risks, along with the uncertainties on the findings from clinical trials and observational studies on mortality, should be appropriately reflected through warnings and recommendations in the product information and captured in the risk management plan.

All risks of aprotinin known to date were considered. There is no evidence of an association between aprotinin and perioperative mortality from randomised clinical trials when the BART study is excluded. The observational studies have provided conflicting results related to mortality as discussed above. Reduction in massive bleeding, transfusion need and risk for re-surgery due to bleeding are considered meaningful clinically important effects of aprotinin, and when considering the overall data on the known risks, the CHMP considered that the balance is clearly positive in the identified patient population. Re-surgery due to bleeding carries high risk for increased morbidity which also was emphasised by the group of external experts consulted by the CHMP. The reduction of the need for re-surgery after coronary artery bypass grafting (CABG) demonstrated for aprotinin is considered to be a benefit of high clinical relevance. Therefore, taking the totality of data into account it is judged that the previous signal for an increased mortality associated with the use of aprotinin is refuted provided that aprotinin is given in the identified target population and the recommendations for its use are followed. In this regard, a study on the profile of aprotinin use is needed, particularly in light of the importance of adequate anticoagulation. The CHMP considered that a registry should be conducted by MAHs of aprotinin containing medicinal products affected by this review. The registry, which will be mandatory for use of the product, will monitor the pattern of use in participating countries and record utilisation information. The number of patients who receive aprotinin, indication for administration, patient characteristics and risk factors and conditions of use including data on heparinisation of patients treated with aprotinin are some of the information to be collected. The MAHs will submit a revised protocol for the registry to national competent authorities.

Taking into account all the data available on the efficacy and safety of aprotinin to date, the CHMP considered that there is clear evidence of a patient population in which the efficacy of systemic aprotinin clearly outweighs its risks. The proposed indication is 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).

As a result, the Committee agreed on the lifting of the suspension for aprotinin with the balance of risks and benefits considered positive in the following revised indication for aprotinin:

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).

Divergent positions are appended to the Opinion.

A direct healthcare professional communication (DHPC) was agreed to provide prescribers with information on the review and an update on the safety information for aprotinin.

Grounds for lifting of the suspension and amendment of the marketing authorisations of aprotinin containing medicinal products listed in Annex I

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, for aprotinin, aminocaproic acid and tranexamic acid (see Annex I).

- The Committee considered all data provided by the MAHs in writing and at the oral explanation, including data available from literature reviews and the outcome of a scientific advisory group.

- The Committee concluded that evidence from randomised clinical trials and observational studies support the use of aprotinin in reducing the incidence of massive bleeding, the need for transfusion of blood products and the need for re-surgery for bleeding.

- The CHMP concluded that the BART data and the signal on increased mortality associated with aprotinin compared to EACA and TXA were not considered reliable, based on the totality of evidence now available since the review of aprotinin undertaken in 2007, including more recent observational studies, the new analyses of the BART study data and the identified major study flaws, and taking the advice of the SAG into account. The CHMP noted that since the initial review in 2007, more data has become available, such as new observational studies, the final study results of the BART study, and more importantly new analyses of the BART study. These new data have now made it possible to identify the major flaws of the BART study, not identifiable before.

- The Committee considered that the available randomised clinical trial and meta-analysis of clinical trials (when the BART study is excluded) do not give evidence of an association between aprotinin and perioperative mortality. No firm conclusion on cardiovascular risks can be made on the BART study due to several serious methodological issues identified. In addition, results from observational studies are conflicting. Taking the totality of data into account it is judged that the previous signal for an increased mortality associated with the use of aprotinin should be refuted provided that the drug is given in the identified target population of adult patients at high risk of major blood loss undergoing isolated coronary artery bypass graft (CABG) surgery and the recommendations for its use are followed.

- The Committee considered that the product information should be updated to ensure that the information to healthcare professionals and patients is up-to-date. Recommendations on adequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure should be reflected in the product information. Special attention is also to be given to patients with renal impairment and to the possible occurrence anaphylactic reactions. All risks should be captured in the risk management plan. In addition, a registry must be conducted by MAHs of aprotinin containing medicinal products in order to gather more information on the profile of aprotinin use. A restricted distribution of aprotinin is envisaged with aprotinin available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry.

Therefore the CHMP concluded that the balance of risks and benefits for aprotinin is positive under normal conditions of use subject to the revision of the indication as follows:

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).

On the basis of the above, the Committee recommended the lifting of the suspension and the amendment of the marketing authorisations for the medicinal products containing aprotinin referred to in Annex I for which the amendments to the product information are set out in annex III of the opinion.

The scientific conclusions and the grounds for the lifting of the suspension and amendment of the marketing authorisation are set out in annex II of the opinion.

The conditions with regard to the safe and effective use of the medicinal product to be implemented by the member states are set out in annex IV of the opinion.

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_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 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, 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 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: ≥ 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
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	***Anaphylactic shock (potentially life threatening)***
Blood and lymphatic system disorders				***Disseminated intravascular coagulation*** ***Coagulopathy***
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)	***Pulmonary embolism***
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:

In-hospital Mortality in a 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)

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 $_{131}$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.

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

<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>

<u>For adult patients the following dose regimen is recommended:</u>

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_1-antagonist and a H_2-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]

Annex IV

Conditions of the marketing authorisations

National Competent Authorities shall ensure that the following conditions are fulfilled by the MAHs of aprotinin containing medicinal products:

1. Marketing authorisation holders of aprotinin containing medicinal products shall submit to the national competent authorities, further to the issuing of the Commission Decision and prior to re-launch of the medicinal product to the European market, an update of the risk management plan (RMP) referring to the agreed products' safety concerns as described in the assessment report of the referral procedure and their risk minimisation which includes a direct healthcare professional communication. This RMP shall follow the EU RMP template and shall include the measures to assess the effectiveness of the risk minimisation.

2. Marketing authorisation holders shall conduct a registry, in order to monitor the pattern of use of aprotinin. The registry shall record utilisation information on patients at cardiac surgery centres exposed to aprotinin in participating countries. It shall thus be set up in advance of placing the product on the market. The MAH shall take due account of the draft protocol and comments received during assessment. The registry's protocol shall be submitted to the national competent authorities within 2 months of Commission Decision. Updates on the registry will be submitted to national competent authorities with periodic safety update reports (PSURs).

3. A restricted distribution of aprotinin with the above mentioned registry, with aprotinin available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry.