EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid

aprotinin

Procedure number: EMEA/H/A-1267

Referral under Article 31 of Directive 2001/83/EC

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 12 March 2010, Germany triggered a referral under Article 31 of Directive 2001/83/EC. The Committee for medicinal products for human use (CHMP) was requested to give its opinion on whether the marketing authorisations for medicinal products containing aprotinin, aminocaproic acid and tranexamic acid should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

2.1. Introduction

Antifibrinolytics[1] (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 2006 concerns were raised over the safety of aprotinin as a result of the publication of observational studies (Mangano *et al* 2006, Karkouti *et al* 2006) and the preliminary results of a large observational cohort study (i3 Drug Safety, 2007). These found an increased risk in renal dysfunction and/or cardiovascular events in patients treated with aprotinin compared to those treated with EACA or TXA. In 2007 preliminary results of a randomised controlled clinical trial, the 'Blood conservation using antifibrinolytics: a randomised trial in a cardiac surgery population' (BART) study, become available. The BART was a prospective, randomised, blinded trial in patients undergoing a procedure for which cardiopulmonary bypass (CPB) was required. It was designed to determine whether aprotinin was superior to EACA and TXA in decreasing the rate of massive bleeding and the need for transfusions. The preliminary results of the BART study showed that although the use of aprotinin was associated with less serious bleeding than either of the comparator drugs, more deaths due to haemorrhage had been observed among patients receiving aprotinin. The BART study was discontinued due to the safety signal. In November 2007, based on the review of available data[2] at the time, including the preliminary results of the BART study, the CHMP concluded that the benefit/risk balance of aprotinin-containing medicinal products for systemic use was not favourable. The marketing authorisations for all aprotinin-containing medicines in the European Union were suspended with a condition for marketing authorisation holders (MAHs) to identify a patient population in which the efficacy of systemic aprotinin clearly outweighed its risks. In its 2007 review, the Committee also acknowledged the need to trigger an article 31 referral procedure in order to evaluate the totality of the information on the BART study, once the final report would be available.

Further to the publication of the final results of the BART study an overall review on the benefits and risks of antifibrinolytics was considered necessary. In March 2010 Germany triggered this article 31 referral to assess the benefits and risks of the antifibrinolytic drugs aprotinin, EACA and TXA in all its approved indications.

Several data sources informed the opinion of the Committee, including available data from clinical studies, published literature, spontaneous reports and other data submitted by MAH's 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 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 a summary on the BART study and the discussion and conclusions on aprotinin. For details on EACA and TXA please refer to their respective reports.

[1] Fibrinolysis is degradation of intravascular fibrin clots by action of plasmin that results from plasminogen hydrolysis.
[2] The initial 2007 review was handled under Article 107(2) of Directive 2001/83/EC.

2.2. Clinical aspects

2.2.1. BART study

The BART study[3] was a prospective, multicentre, randomised double blinded trial involving 'high-risk' cardiac surgery patients, i.e., defined as surgical intervention with an average mortality of at least twice the norm for isolated primary coronary artery bypass graft (CABG) and a risk of repeat surgery exceeding 5%. The study was designed to compare the therapeutic use of aprotinin with EACA and TXA. The study was administered by the Ottawa Health Research Institute (OHRI), with patients enrolled at several centres across Canada.

The patient population was not limited to the approved indication and consisted of high-risk cardiac surgical patients requiring one of the following high-risk surgical interventions, either on an elective or urgent basis; all surgery had to be done on cardiopulmonary bypass (CPB):

- Re-operation for CABG;
- Re-operation for aortic valve replacement;
- Re-operation for mitral valve replacement or repair;
- Initial mitral valve replacement;
- Aortic and/or mitral valve replacement/repair with a CABG;
- Multiple valve replacement/repair (initial or re-operation);
- Ascending aortic artery procedures (including Bental procedures, etc).

The protocol-specified primary outcome was massive postoperative bleeding. Secondary outcomes included allogeneic exposure to any blood product, fatal/life-threatening event (e.g. 30-day all-cause mortality, myocardial infarction (MI) and cerebrovascular accidents) and serious adverse events (e.g. dialysis-dependent renal failure, need for prolonged invasive mechanical ventilatory support (greater than 48 hours) or prolonged low output state (need for vasopressors, balloon pump, or ventricular assist device for more than 48 hours)).

In terms of efficacy, the results of the BART study demonstrated reduced incidence in massive post-operative bleeding and reduced need for transfusion of blood products when aprotinin was used as compared to EACA and TXA. Aprotinin was also superior to both EACA and TXA with respect to avoiding re-operation for bleeding and significant perioperative bleeding from chest tubes in CABG surgery.

Regarding safety, the preliminary results of the BART study had shown that 30-day all-cause mortality in the aprotinin arm was increased in comparison to EACA or TXA. Results were not statistically significant but the trend of an increased mortality in the aprotinin arm was reported as consistent throughout the study.
A new analysis of originally recorded data was undertaken for 30-day all-cause mortality, including all randomised subjects for whom data was available, as shown in the table below.

Treatment group	Number of subjects	30-day deaths	(%)
Aprotinin	809	47	5.8
Tranexamic Acid	808	34	4.2
Aminocaproic Acid	814	32	3.9
Total	2431	113	4.6

Note that 30-day mortality data were not available for 37 randomised subjects: 14 randomised to aprotinin, 14 randomised to tranexamic acid, and 9 randomised to aminocaproic acid.

The relative risk (RR) calculated by the MAH of aprotinin containing medicinal products was 1.48 (95% CI 0.95-2.29, p=0.08) for aprotinin compared with EACA and 1.38 (95% CI 0.90-2.12, p=0.14) for aprotinin compared with TXA. Neither of these results was statistically significant. The numerical difference in mortality between treatment arms was mostly observed during the first 5 days. There were no clear differences for mortality between treatment arms after this period.

Other serious adverse events of interest included as secondary outcomes - stroke, MI and renal failure/dysfunction - did not show any significant differences between the three treatment groups (see table below reporting on 30-day safety outcomes possibly pertinent to mortality).

[3] BART study: Blood conservation using antifibrinolytics: a randomised trial in a high-risk cardiac surgery population, *Fergusson et al* (2008), New England Journal of Medicine.

30-day safety outcomes possibly pertinent to mortality

Outcome (N)	Aprotinin vs. Tranexamic Acid		Aprotinin vs. Aminocaproic Acid	
	RR	*P*-value	RR	*P*-value
Myocardial Infarction[b] (2180)	1.19	0.48	1.61	0.08
Stroke (2280)	0.78	0.37	1.01	0.97
DVT/PE[c] (2161)	1.00	0.79	1.00	0.58
Any thrombotic event[d] (2193)	1.04	0.64	1.40	0.75
Any post-op dialysis	0.99	0.99	1.15	0.63
Renal failure (composite outcome)[b] (2310)	0.94	0.56	0.98	0.87

a Includes for 103 subjects 30-day mortality data not provided in the BART publication. RR and p values calculated by Bayer. 30-day all-cause mortality outcome is missing for 37 subjects.
b Definition as reported in the BART publication and inconsistent with the protocol.
c Outcome not specified in the BART protocol, but reported in the BART publication.
d Outcome specified in the BART protocol, not reported in the BART publication, but reported in the DSMB final report. RR and p-values were calculated by Bayer using data for this outcome reported in the BART DSMB final report.

Although there was no increase in the risk for renal dysfunction or renal failure associated with the use of aprotinin compared to both EACA and TXA, there was an increase in the proportion of patients with a doubling of serum creatinine levels in the aprotinin group.

The new analysis of data available further to finalisation and publication of the final study results also showed that aprotinin prolongs certain measures of blood clotting time. Patients treated with aprotinin had higher recorded values for partial thromboplastin time (PTT) than patients treated with EACA and TXA. In addition, the new analysis also indicated that less heparin had been used in the aprotinin arm compared to EACA and TXA arms, in particular in sites with reported 30-day mortality (compared to sites with no reported mortality). This new evidence raised doubts if the observed trend for differences in mortality disfavouring the aprotinin group could be explained by under-heparinisation and inadequate use of the appropriate method to maintain adequate anticoagulation. In addition, analysis of cause of death for 5-day mortality seemed to also indicate an association between site and mortality, with only a few sites accounting for most of the numerical difference between treatments.

The BART study results did not indicate a clear difference between the risks or benefits of EACA compared to TXA.

During the review of the final results and new analysis of the BART study by the CHMP, concerns were raised regarding aspects of the trial methodology, including unplanned interim analysis, the unjustified exclusion of patients from the outcome analyses, the lack of important data on anticoagulant monitoring and an apparent change in the definition of components of the primary outcome. In addition, subgroup analysis indicated that in some centres with higher mortality rates for aprotinin compared with EACA or TXA, patients treated with aprotinin had lower heparinisation or excessive amounts of protamine had been used.

A scientific advisory group (SAG) meeting was held, mainly to discuss the final results and new analysis of the BART trial and provide views on the use of aprotinin in CABG.
The impact of aprotinin in the reduction of massive bleeding was considered of clinical relevance by the SAG. Although the link between blood loss and mortality has not been proven, bleeding less would result in fewer complications, fewer transfusions and less time spent in hospital, which was considered clinically relevant.
Regarding heparinisation, the SAG considered that the use of non-appropriate activated clotting tests at some of the centres might have influenced the level of heparinisation of patients, i.e., under-heparinisation of patients randomised to aprotinin, resulting in differences in outcome of cardiovascular surgery in terms of mortality and morbidity at different centres. In addition, the increase in mortality could also be influenced by differences in baseline patient characteristics and centre variability.
Overall the SAG considered that the BART study had major flaws, such as the unexplained exclusion of patients from the final study results, underlying differences in baseline characteristics between the study groups which were not homogenous in spite of randomisation, and the reduced level of heparinisation in the aprotinin arm which would increase the risk of thrombogenic events in this group. Therefore the SAG experts agreed that the BART data and the signal of increased mortality in the aprotinin arm were not considered reliable.

The CHMP noted that since its 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.

2.2.2. Aprotinin

Aprotinin was only indicated in CABG surgery. No other indications were considered for this review. Details of the assessment can be found hereinafter.

Two MAHs submitted data for review. An overview of the evidence of therapeutic benefit of aprotinin from randomised clinical trials and observational studies, including meta-analysis, available to date was provided and considered for the assessment. Only relevant information for the discussion is presented hereinafter.

Efficacy

BART study
The results of the BART study (see also section 2.2.1 Bart study) suggested that use of aprotinin was associated with a lower risk of massive bleeding than either TXA or EACA.

Other randomised trials and observational studies
An overview of the evidence of therapeutic benefit of aprotinin from randomised clinical trials and observational studies, including new meta-analysis published after the preliminary BART results, was provided.
The efficacy results observed in the BART study were consistent with results from other randomised clinical studies and observational studies. Results of clinical studies demonstrate statistically significant reductions in blood loss and donor blood transfusion requirements when aprotinin is administered to patients undergoing cardiac surgery requiring CPB. The number of patients that was considered to be in need of blood transfusion was reduced from 53% in the placebo groups to 37% with aprotinin in the pooled clinical trial data set. It has also been demonstrated that aprotinin reduces the risk for re-operation for bleeding. In direct and indirect comparisons with lysine analogues it seems that aprotinin is more effective in prevention of bleeding.

The following tables present a summary of the available data on the efficacy of aprotinin. The primary CABG trials are summarised in the first table presented below. The second table summarises the trials in repeat CABG surgery.

Randomised, double-blind, placebo-controlled trials in primary CABG

Study (Principal Investigator)	Surgical Procedure	Number of Patients Evaluated for Efficacy			
		Total	Placebo	Half-dose Aprotinin	Full-dose Aprotinin
448 (*Lemmer*)	Primary CABG	141	67	NA	74
	Repeat CABG	55	32	NA	23
457 (*Levy*)	Primary OHS	54	17	18	19
	Primary CABG[a]	18	5	7	6
	Repeat OHS	38	12	14	12
	Repeat CABG[a]	17	7	4	6
471 (*Lemmer*)	Primary CABG	644[b]	157	168	160
472 (*Alderman*)	Primary CABG	796	395	NA	401

Abbreviations: CABG = coronary artery bypass graft; NA = not applicable; OHS = open heart surgery
a This group is a subset of the overall study population.
b This study was the only study to include the pump-prime dose regimen with 159 patients valid for efficacy.

Randomised, double-blind, placebo-controlled trials in repeat CABG

Study (Principal Investigator)	Surgical Procedure	Number of Patients Evaluated for Efficacy			
		Total	Placebo	Half-dose Aprotinin	Full-dose Aprotinin
447 (Cosgrove)	Repeat CABG	154	52	49	53
448 (Lemmer)	Primary CABG	141	67	NA	74
	Repeat CABG	55	32	NA	23
457 (Levy)	Primary OHS	54	17	18	19
	Primary CABG[a]	18	5	7	6
	Repeat OHS	38	12	14	12
	Repeat CABG[a]	17	7	4	6
466 (Levy)	Repeat CABG	254[b]	65	60	61

Abbreviations: CABG = coronary artery bypass graft; NA = not applicable; OHS = open heart surgery
a This group is a subset of the overall population.
b This study was the only repeat CABG study to also include the pump-prime dose regimen with 68 patients valid for efficacy.

The efficacy in blood loss and transfusion requirements is shown in the tables below, in primary CABG (first table) and in repeat CABG (second table).

Efficacy variables in the primary CABG Patient Pool

Variable	**Placebo N = 624**	**Aprotinin Full-Dose N = 641**
% of patients who required donor red blood cells	53.5%	36.8%[a]
% patients who required 5 or more units of red blood cells	10.1%	2.8%[a]
% patients who required donor platelets	17.6%	4.1%[a]
Mean (SD) units of donor blood transfused	1.7 (2.4)	0.9 (1.4)[a]
Mean (SD) mL of donor blood transfused	584 (840)	295 (503)[a]
Mean (SD) platelets transfused (donor units)	1.3 (3.7)	0.3 (1.5)[a]
Mean (SD) cryoprecipitate transfused (donor units)	0.5 (2.2)	0.0 (0.0)[a]
Mean (SD) fresh frozen plasma transfused (donor units)	0.6 (1.7)	0.2 (0.9)[a]
Mean (SD) thoracic drainage rate (ml/h)	87 (67)	39 (32)[a]
Mean (SD) total thoracic drainage volume (ml)[b]	1,232 (711)	705 (493)[a]
% of patients requiring re-operation for diffuse bleeding	1.4%	0%[b]

Abbreviations: SD = standard deviation
a Significantly different from placebo, $P < 0.05$ (transfusion variables analysed via ANOVA on ranks).
b Excludes patients who required re-operation.

Efficacy variables in the repeat CABG Patient Pool

Variable	Placebo N = 156	Aprotinin Full-Dose N = 143
% of patients who required donor red blood cells	76.3%	46.9%[a]
% of patients who required 5 or more units of red blood cells	27.6%	8.4%[a]
% patients who required donor platelets	44.9%	8.4%[a]
Mean (SD) units of donor blood transfused	3.7 (4.4)	1.6 (2.9)[a]
Mean (SD) mL of donor blood transfused	1,132 (1443)	515 (999)[a]
Mean (SD) platelets transfused (donor units)	5.0 (10.0)	0.9 (4.3)[a]
Mean (SD) cryoprecipitate transfused (donor units)	0.9 (3.5)	0.1 (0.8)[a]
Mean (SD) fresh-frozen plasma transfused (donor units)	1.3 (2.5)	0.2 (0.9)[a]
Mean (SD) thoracic drainage rate (ml/h)	89 (77)	40 (36)[a]
Mean (SD) total thoracic drainage volume (ml)[b]	1,659 (1226)	960 (849)[a]
% of patients requiring re-operation for diffuse bleeding	1.9%	0%

Abbreviations: SD = standard deviation

a Significantly different from placebo, $P < 0.05$ (transfusion variables analysed via ANOVA on ranks).

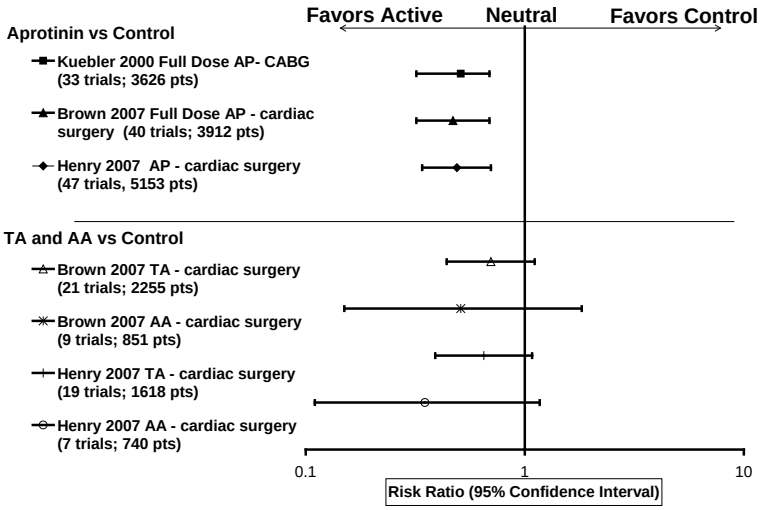
b Excludes patients who required re-operation.

Results from recent reviews (*Henry et al*) indicate that in cardiac surgery aprotinin reduced the need for re-operation due to bleeding compared to placebo or no treatment by a relative 54% (RR 0.46; 95% CI 0.34-0.63) and exposure to allogeneic blood by a relative 32% (RR 0.68; 95% CI 0.63-0.73). According to the most recent review aprotinin was more effective than the pooled lysine analogues in reducing the need for any allogeneic blood transfusion in cardiac surgery (RR 0.86; 95% CI 0.76-0.96). In all surgeries there was a trend favouring aprotinin with respect to the need for re-operation for bleeding compared to TXA (RR 0.69; 95% CI 0.51-0.93) and also compared to EACA (RR 0.70; 95% CI 0.49-1.00).

Potential for decreased mortality for patients requiring re-exploration for bleeding

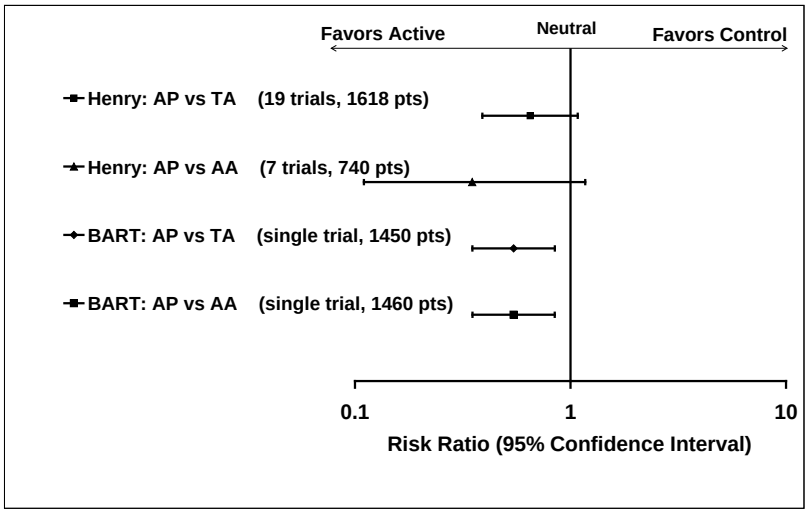
Results from three meta-analysis revealed a consistent increase (3-fold to 4-fold) in mortality for patients requiring re exploration for bleeding (4.8%) when compared to patients not requiring re-exploration (1.2%),[*Moulton et al.*, n=6015] from 3.3% to 9.5% [*Dacey L.J. et al*., n=8586], and from 5.5% to 22% [*Unsworth-White, M.J., et al*., n=2221], respectively. It is not the re-exploration per se, but more importantly the degree of bleeding that usually necessitates re-exploration which probably results in a negative outcome. The analysis by *Moulton et al* revealed that when patients bleed more than 1500 ml to 2000 ml within 24 hours, there is an exponential increase in the percentage of patients who develop adverse outcomes and an increase in mortality (12.1% in patients with > 2,000 ml vs. 4.3% in patients with < 2,000 ml blood loss). In these analyses, approximately 50% of patients who had excessive bleeding requiring re-exploration had a surgical source of bleeding, which may demonstrate the important role of acquired haemostatic abnormalities that result in diffuse, microvascular bleeding and that can be attenuated by pharmacologic therapy.

The figure below indicates that in the meta-analyses shown, aprotinin significantly reduced the risk for re-exploration compared to the control group. In contrast, a significant reduction in the re-operation rate was not observed for tranexamic acid and aminocaproic acid in comparison to their respective control groups.



Control group is a randomised group other than aprotinin, tranexamic acid or aminocaproic acid, generally placebo.

As shown, the meta-analysis referred below reviewed 47 trials for the risk of re-exploration.[*Henry et al*, 2007, n=5153]. The use of aprotinin significantly reduced re-explorations for bleeding by 51% (RR = 0.49; 95% CI 0.34-0.70). This meta-analysis also summarised the efficacy of aprotinin versus tranexamic acid and aminocaproic acid. As shown in the figure below there was a trend favouring aprotinin with respect to the need for re-operation for bleeding.

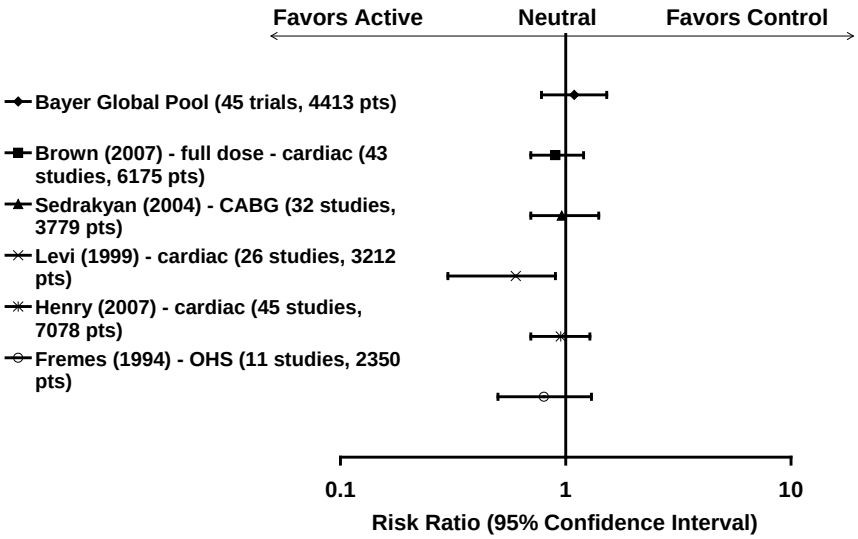


Safety

Regarding safety, and in particular the perioperative mortality risk, an overview of the data available to date from randomised controlled trials and observational studies was reviewed.

In the MAH's clinical trial database, 2.9% of aprotinin patients and 2.5% of placebo patients died (regardless of time interval after dosing). The numerical imbalance was due to the findings in one study in repeat CABG where insufficient heparinisation at some centres was reported. Most deaths were attributed to cardiac conditions in both groups, as can be expected. Coronary artery bypass grafting (CABG) has a high incidence of cardiac and surgical procedure-related adverse events. There was no difference in death rates (risk ratio 1.09; 95% CI 0.78-1.52). These findings were consistent with those reported in the literature. The figure below summarises the results from meta-analysis of randomised studies comparing aprotinin with placebo or no treatment.

Perioperative mortality risk as estimated in meta-analyses



Control group is randomised group other than aprotinin, tranexamic acid or aminocaproic acid; generally placebo

Prior to the publication of the BART trial, randomised clinical trial data did not significantly show an increase of the risk of MI, stroke, renal dysfunction or overall mortality for aprotinin compared to placebo. There was a slightly increased incidence in mortality in the MAHs trial database (RR=1.09) with aprotinin relative to placebo. However, the increased risk was mainly observed in repeat CABG, and was due to a numerical imbalance in one study, where differences in heparinisation were also reported. Other published meta-analyses suggest a slightly decreased risk (RR/OR = 0.55 - 0.96).

The updated meta-analysis of *Henry et al* 2011 compared aprotinin to EACA or TXA concerning all-cause mortality. The results showed a statistically increased mortality with aprotinin (RR 1.39; 95%CI 1.02-1.89) but it was mainly driven by the BART study data. As indicated before, and confirmed by the expert SAG panel, the BART trial results were not considered reliable following review of the evidence available to date. When excluding the BART trial, the findings from randomised clinical trials give no evidence of an association between aprotinin and perioperative mortality.

Available comparative results of aprotinin against other antifibrinolytics are also reassuring. In head-to-head comparisons between aprotinin and TXA, there was no statistically significant difference in mortality, MI, stroke or renal failure/dysfunction. There were also no statistically significant differences between aprotinin and EACA or TXA and EACA in head-to-head comparisons of mortality and MI.

The available observational studies were discussed in relation to perioperative mortality. From the initial observational studies which were referred in the previous review, it is worth nothing the weight of evidence available today, and to put this evidence in perspective in absence of supporting data from randomised clinical trials. The FDA made re-analysis of *Mangano et al*, in-hospital data. The results gave a statistically significant association between aprotinin (compared to no treatment) and dialysis, but no statistically significant association between aprotinin treatment and myocardial infarction, congestive heart failure, stroke or in-hospital death. In the study by *Karkouti et al*, results were consistent with those observed in clinical trials, demonstrating the known effect of aprotinin on renal function (transient rise in serum creatinine) and again no statistically significant association between aprotinin treatment and myocardial infarction, stroke or in-hospital death. The findings from the i3 Drug safety study are surrounded by methodological questions, considering that an association was reported initially between aprotinin and perioperative mortality, but a supplementary analysis of the data provided by the investigators to the MAHs gave a non-significant association between aprotinin and 7-day in-hospital mortality. Whilst the initial concerns were raised by the findings of e.g. Mangano *et al* (2006), Karkouti *et al* (2006), and in particular i3 Drug Safety (2007), it is noted that considering the inherited studies' limitations and following re-analysis of some of the data, there is no evidence of a statistically significant association between aprotinin and perioperative mortality. It is to be noted that other more recent studies , e.g. *Coleman et al* (2007), *Pagano et al* (2008), *Ngaage et al* (2008) and *Karkouti et al* (2009) concluded that aprotinin did not affect in-hospital mortality, with *Karkouti* reporting a statistically significant mortality 'benefit' for aprotinin in high-risk cardiac surgery patients, compared with TXA. The risk of perioperative mortality in the cardiac surgery population overall (aprotinin compared with TXA) was 0.95, p=0.80; the risk of perioperative mortality in the high-risk subgroup was 0.60, p=0.05.

Other observational studies dealing with a possible association between aprotinin and long-term mortality e.g. *Shaw et al* (2008), *Olenchock et al* (2008) suggested an increased risk for long-term mortality. Considering the limitations inherent to observational studies, the results may be confounded, with no control for baseline differences and loss to follow-up. In addition to methodological criticism, the reported magnitude of the association from these studies is low and must therefore be interpreted with caution. The limitations inherent to observational studies were noted by the CHMP.
The tables below summarise the results from observational studies (perioperative and long-term mortality).

Observational studies: perioperative mortality

Study	Treatment (N)	Covariates[a] Adequate	Balance	Reported Association
Mangano, 2006 FDA Re-analysis (All CABG 1996 – 2000)	Aprotinin 1295 No treatment 1374	No	Suboptimal; not balanced for center, surgeon, year	0.91 (0.54-1.53) RR
Karkouti, 2006 (High risk cardiac surgery 1999-2004)	Aprotinin 449; Tranexamic acid 449	Unknown	Balanced except for year of surgery	0.90 (0.54-1.51) RR
i3 Drug Safety, 2006 Preliminary[b] FDA Reanalysis (All CABG 2003-2006)	Aprotinin 29,358; Other antifibrinolytic 37,077	No	Suboptimal; not balanced for center, surgeon, year	1.54 (1.38-1.73) OR
Coleman, 2007 (All CABG 2000-2005)	Aprotinin 362; Control (no aprotinin) 2,986	No	Unknown	0.85 (0.52 - 1.40) OR
Pagano, 2008 (Cardiac surgery 1998-2006)	Aprotinin 3,481 No Aprotinin 4,355	Unknown	Unknown	1.03 (0.71-1.49)[c] OR
Ngaage, 2008 (CABG, Valve surgery or both)	Aprotinin 3334, No aprotinin 3417 (Logistic Regression)	Unknown	Unknown	0.96 (0.64-1.43) OR
Ngaage, 2008 (CABG, Valve surgery or both)	Aprotinin 341, No aprotinin 341 (Propensity-matched)	No	Not balanced for surgeon, year of surgery	"Evenly distributed"; p=0.36[d]
Karkouti, 2009 (High risk cardiac surgery 2000-2008)	Aprotinin 772; Tranexamic acid 772	Unknown	Balanced except for year of surgery	0.95 (0.66-1.36) RR

a Baseline variables, e.g., clinical risk factors, centre, procedure, surgeon
b i3 Drug Safety studies (administrative database) did not distinguish on- and off-pump surgeries.
c For isolated CABG odds ratio was 1.01 (0.54-1.88); Aprotinin N=1982; No aprotinin, N=3421
d Overall mortality 2% for the aprotinin group, 1% in the no aprotinin group; p=0.36; confidence intervals not reported.

Observational studies: long-term mortality

Study	Treatment (N)	Covariates[a] Adequate	Balance	Reported Association
Mangano, 2007 FDA Reanalysis (All CABG, 1996-2000)	Aprotinin 1277; No treatment 1238	No	Suboptimal, not balanced for center, surgeon, year	1.39 (1.05-1.84) (at year 4)
Shaw, 2008 (All CABG, 1996-2005)	Aprotinin 1,343; Aminocaproic Acid 6,776; No Treatment 2,029	No	Demonstrably Imbalanced	1.27 (1.10-1.46) vs. Aminocaproic acid 1.32 (1.12-1.55) vs. No treatment
Pagano, 2008 (Cardiac Surgery 1998 - 2006)	Aprotinin 3,481 No Aprotinin 4,355	Unknown	Unknown	1.09 (0.93-1.28)
Olenchock, 2008 (Isolated CABG 1994-2006)	Aprotinin 1,507; Aminocaproic acid 1,830	Unknown	Unknown	1.62 (1.39-1.90)

[a] Baseline variables, e.g., clinical risk factors, centre, procedure, surgeon.

Adverse events of special interest

The safety data considered included in-depth discussions on adverse events of special interest, such as those affecting the cardiac and renal function. Data on thromboembolic events, renal safety, mechanisms of potential renal dysfunction developing during the clinical use of aprotinin, the summary of intra-renal hemodynamic effects of aprotinin administration in man, renal tubular biochemical and functional effects of aprotinin administration in man, pre-existing renal functional impairment, and mechanisms whereby concurrent drug administration may enhance aprotinin induced renal dysfunction were considered.

The distribution of spontaneous reports (including those with fatal outcomes) across the different system organ classes (SOCs) in patients treated with aprotinin is given in the table below. For the period between 1985 and 2010 the highest proportion of events from patients in whom death has been reported accumulates in the SOC Cardiac disorders (27.6%). The fatal events in order of frequency by SOC are cardiac disorders (27.6%); vascular disorders (12.3%), respiratory, thoracic and mediastinal disorders (8.8%); general disorders and administration site conditions (6.8%).

Spontaneous reports of adverse events classified by MedDRA[4] System Organ Class

System Organ Class	Fatal (N events = 1555)		All (N events = 3380)	
Blood and lymphatic systems disorders	75	(4.8%)	122	(3.6%)
Cardiac disorders	429	(27.6%)	686	(20.3%)
General disorders and administration site conditions	105	(6.8%)	139	(4.1%)
Immune system disorders	80	(5.1%)	407	(12.0%)
Injury, poisoning and procedural complications	78	(5.0%)	160	(4.7%)
Investigations	88	(5.7%)	313	(9.3%)
Nervous system disorders	49	(3.2%)	126	(3.7%)
Renal and urinary disorders	98	(6.3%)	215	(6.4%)
Respiratory, thoracic and mediastinal disorders	137	(8.8%)	290	(8.6%)
Skin and subcutaneous tissue disorders	25	(1.6%)	108	(3.2%)
Vascular disorders	192	(12.3%)	454	(13.4%)

In addition to mortality, other adverse events of special interest such as thromboembolic events, renal impairment and hypersensitivity were also considered by the CHMP.

[4] MedDRA is the Medical Dictionary for Regulatory Activities. It is the clinically validated terminology used to report adverse event data from clinical trials, and for post-marketing reports and pharmacovigilance.

During open heart surgery by CPB, an increased risk for thromboembolic events may be expected. No increased risk of aprotinin with respect to thromboembolic events was observed in randomised clinical trials or observational studies. The overall risk of MI with aprotinin does not seem to differ significantly from placebo.
The results from observational studies showed that the risk of perioperative mortality in the cardiac surgery population overall (aprotinin compared with TXA) was 0.95, p=0.80; the risk of perioperative mortality in the high-risk subgroup was 0.60, p=0.05. Some results of observational studies were conflicting, and the limitations of such studies were clearly noted above. The incidence of stroke was numerically lower in the aprotinin groups than in the placebo groups in pooled clinical data.

The renal effects of aprotinin are known. Data available indicate that transient renal impairment is a well characterised unfavourable effect of treatment with aprotinin. This is important in particular for patients with known pre-existing impairment and in patients concomitantly treated with drugs that may affect renal function.

The risk of hypersensitivity reactions to aprotinin are a known unfavourable effect that primarily occurs after repeated treatment.

Discussion on aprotinin

Disease setting
Coronary artery bypass grafting (CABG) has a high incidence of cardiac and surgical procedure-related adverse events. The underlying atherosclerotic cardiovascular disease is often associated with metabolic disease, diabetes mellitus, and hypertension, which are among its main risk factors. These may secondarily lead to renal and hepatic dysfunction and thromboembolic complications with consequential end organ damage. Patients who are scheduled for CABG surgery are often polymorbid with multiple organ functional deficits and limited compensatory potential that make them particularly vulnerable to the development of complications. According to the US Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database, of 503,478 CABG procedures, CABG has a mortality rate of 3.05% and a major complication rate of 13.40%. Major complications include stroke (1.63%), renal failure (3.53%), re-exploration for bleeding (5.17%), prolonged ventilation (5.96%), and sternal infection (0.63%).
The nature of the disease and the risks associated with the procedures used to address it must be taken into consideration when assessing treatment options.

Benefits
In terms of efficacy, randomised clinical studies' results (including the BART trial) and observational studies have been consistent.
Results of clinical studies demonstrate statistically significant reductions in blood loss and donor blood transfusion requirements when aprotinin is administered to patients undergoing cardiac surgery requiring CPB. The number of patients that was considered to be in need of blood transfusion was reduced from 53% in the placebo groups to 37% with aprotinin in the pooled clinical trial data set. It has also been demonstrated that aprotinin reduces the risk for re-operation for bleeding.

The impact of aprotinin in the reduction of massive bleeding was considered of clinical relevance by the SAG. Bleeding less would result in fewer complications, fewer transfusions and less time spent in hospital, which was considered clinically relevant.

Overall data consistently show that aprotinin reduces the incidence of massive post-operative bleeding and reduces the need for transfusion of blood products as compared to EACA and TXA. Aprotinin was also superior to both EACA and TXA with respect to avoiding re-operation for bleeding and significant perioperative bleeding from chest tubes in CABG surgery.

Risks
In terms of cardiovascular safety concerns, the BART study initially reported an increase in 30-day all-cause mortality in the aprotinin group as compared to EACA and TXA. The excess in deaths in the aprotinin group appeared to be attributable to an increase in cardiac mortality.
However, further to the publication of the final results, several concerns were raised regarding aspects of the analysis of the BART study, including unplanned interim analysis, the unjustified exclusion of patients from the outcome analyses, the lack of important data on anticoagulant monitoring and an apparent change in the definition of components of the primary outcome. In addition, new subgroup analysis indicated that in some centres with higher mortality rates, patients treated with aprotinin had lower heparinisation or excessive amounts of protamine had been used, when compared to EACA and TXA patients. This was particularly evident in centres with reported 30-day mortality (compared to the

sites with no reported mortality). Different methods used for monitoring the anticoagulative effects could be a reasonable explanation for the differences in doses observed. The CHMP noted that inadequate heparinisation and/or excessive amounts of protamin could be expected to lead to an increased risk for thrombogenic events. Overall, the BART study was not adequately designed or powered for the secondary endpoint 'all-cause mortality', with several weaknesses identified which impair the conclusion of the study. It has to be 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 all other available randomised clinical trial data (excluding the BART trial) did not significantly show an increase of the risk of MI, stroke, renal dysfunction or overall mortality for aprotinin compared to placebo. A slightly increased incidence of mortality with aprotinin relative to placebo is observed in the MAH for aprotinin containing medicinal products trial's database (RR= 1.09, 95% CI 078-1.52). However, the risk was primarily seen in repeat CABG and was due to a numerical imbalance in one study, where insufficient heparinisation at some centres was also reported. Also of note, repeat cardiac surgery is inherently more technically demanding than primary surgery, as sternal re-entry, pericardial adhesions, in situ arterial grafts, and patent atherosclerotic vein grafts increase the complexity of the procedure. There may be an increased morbidity and mortality of repeat CABG relative to primary CABG surgery.

With regards to the observational studies, the CHMP noted that in the initial review in 2007 concerns had also been raised by the findings of e.g. Mangano *et al* (2006), Karkouti *et al* (2006), and i3 Drug Safety (2007). The *Mangano* results were reanalysed by the FDA and showed that there was no statistically significant association between aprotinin treatment and myocardial infarction, congestive heart failure, stroke or in-hospital death. In *Karkouti et al*, no statistically significant association between aprotinin treatment and myocardial infarction, stroke or in-hospital death was observed. The *i3 Drug Safety* trial results are questioned, as methodological questions have been raised, with an association reported initially between aprotinin and perioperative mortality, whereas a supplementary analysis of the data showed a non-significant association between aprotinin and 7-day in-hospital mortality. Other observational studies dealing with a possible association between aprotinin and long-term mortality e.g. *Shaw et al* (2008), *Olenchock et al* (2008) suggested an increased risk for long-term mortality. Considering the limitations inherent to observational studies, the results may be confounded, with no control for baseline differences and loss to follow-up. In addition to methodological criticism, the reported magnitude of the association from these studies is low and must therefore be interpreted with caution. The CHMP further noted that other recent studies, e.g. *Coleman et al* (2007), *Pagano et al* (2008), *Ngaage et al* (2008) and *Karkouti et al* (2009), concluded that aprotinin did not affect in-hospital mortality, with *Karkouti* reporting a statistically significant mortality 'benefit' for aprotinin in high-risk cardiac surgery patients, compared with TXA. The risk of perioperative mortality in the cardiac surgery population overall (aprotinin compared with TXA) was 0.95, p=0.80; the risk of perioperative mortality in the high-risk subgroup was 0.60, p=0.05. It is the CHMP's view that there is no evidence of an association between aprotinin and perioperative mortality based on the totality of the evidence available to date from randomised clinical trials, when the BART study is excluded. Results from observational studies, where some reported an increase in mortality and others not, while some studies reported a decrease in mortality for patients treated with aprotinin compared to alternatives are of interest. These divergences may relate to comparisons between non-randomised populations e.g. aprotinin use in patients who had more risk factors for increased mortality before surgery than patients in the other treatment groups. Other aspects complicating the interpretation of some observational studies are the use of aprotinin in indications which are not authorised, or inappropriate follow-up treatment in terms of adequate coagulation and heparinisation. The data from these observational studies in isolation, do not allow us to establish or refute an association between aprotinin and increased (or decreased) mortality. Focusing on totality of the risks, the results from these observational studies serve primarily to generate hypotheses that need to be balanced by taking the totality of data into account including all available randomised studies and the long-standing clinical experience with aprotinin.

Risks associated with the use of aprotinin are well-known and they are judged to be manageable. Overall the CHMP considered that the risk of mortality associated with inadequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure was of concern and therefore adequate risk minimisation measures, e.g. product information wording and communication to healthcare professionals, needed to be implemented. Other notable safety concerns included 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.

Patient population where benefits clearly outweigh the risks
Considering the efficacy and safety data on aprotinin available to date, and the opinion of the SAG, the CHMP considered that there is clear evidence of a patient population in which the efficacy of systemic aprotinin clearly outweighs its risks. In addition, the advice of the PRAC was considered by the CHMP. The proposed indication is as follows:

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).

The CHMP considered that in this patient population, there is no evidence of an association between aprotinin and increased perioperative mortality, provided that due account is taken to the clarifications introduced in the wording of the product information. 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 coronary artery bypass graft surgery 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 their uncertainties. 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.

The 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. However, 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. Therefore, the CHMP considered that a registry should be conducted by MAHs of aprotinin containing medicinal products affected by this review. A draft protocol was considered in the assessment. The registry 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.

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 balance is clearly positive. 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 CABG demonstrated for aprotinin is considered to be a benefit of high clinical relevance.

The CHMP considered that the product information's clinical parts warranted revision to ensure that the information to healthcare professionals and patients is up to date. In particular, focus should be given to the identified risks for transient renal impairment and anaphylactic reactions and the risk of cardiovascular complications due to inadequate heparinisation during CABG. All of these important risks should also be appropriately described in a risk management plan. A communication plan should also be defined.

2.3. Risk management plan

Some MAH's for aprotinin containing medicinal products submitted a risk management plan (RMP), which included a risk minimisation plan. This was considered in the framework of this procedure. For completeness, the full summary of the RMP is shown below; only the relevant issues to this procedure were discussed in this report (see also section 2.2.2 Aprotinin).

Table summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Anaphylaxis	Routine pharmacovigilance	• Collection, processing, analysis, and reporting of adverse event reports. • Cumulative evaluation of cases in each PSUR. • Monitoring of anaphylaxis events in the proposed patient registry • Information on posology and method administration in section 4.2 of the SmPC. • Contraindication in section 4.3 of the SmPC. • Warning in section 4.4 of the SmPC.
Renal failure - Creatinine increase (change of > 0.5 mg/dL above baseline)	Routine pharmacovigilance	• Collection, processing, analysis, and reporting of adverse event reports. • Cumulative evaluation of cases in each PSUR. • Monitoring of renal failure events in the proposed patient registry • Warning in section 4.4 of the SmPC. • Adverse drug reaction information in section 4.8 of the SmPC. • Description of pharmacological properties in section 5.0 of the SmPC.
Embolic and thrombotic events	Routine pharmacovigilance Additional pharmacovigilance	• Collection, processing, analysis, and reporting of adverse event reports. • Cumulative evaluation of cases in each PSUR. • Monitoring of thromboembolic events in the proposed patient registry, with restricted distribution of aprotinin to said centres • Warnings and precautions for use in section 4.4 of the SmPC. • Adverse drug reaction information in section 4.8 of the SmPC. • Distribution of healthcare practionners communications.
Important potential risks		
None identified		
Important potential drug interactions or interactions with products		
Perioperative use of Aminoglycosides (Potential for renal dysfunction when used in conjunction with aprotinin)	Routine pharmacovigilance	• Collection, processing, analysis, and reporting of adverse event reports. • Cumulative evaluation of cases in each PSUR.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		• Monitoring of the concomitant use of aprotinin and aminoglycosides in the proposed patient registry • Warning in section 4.4 of the SmPC.
Test for ACT (Incorrect interpretation of ACT results could result in potential inadequate heparinisation.)	Routine pharmacovigilance	• Collection, processing, analysis, and reporting of adverse event reports. • Distribution of DHPCs to relevant medical institutions and healthcare professionals upon lifting of the marketing suspension of aprotinin. • Monitoring of use of ACT in the proposed patient registry. • Warning in section 4.4 of the SmPC.
Important missing information		
Pregnant or lactating women	Routine pharmacovigilance	• Collection, processing, analysis, and reporting of pregnancy reports. • Cumulative evaluation of cases in each PSUR. • Monitoring of pregnant and lactating women in the proposed patient registry • Fertility, pregnancy and lactation information in in section 4.6 of the SmPC.
Previous sensitization to fibrin exposure in reference to anaphylaxis	Routine pharmacovigilance	See identified risk: Anaphylaxis
Re-exposure to aprotinin	Routine pharmacovigilance	See identified risk: Anaphylaxis

The CHMP considered the PRAC advice received regarding the identified risk minimisation measures. In this regard, all MAHs for aprotinin containing medicinal products need to submit an updated risk management plan before re-launch of the product to the EU market. The MAHs shall update all relevant sections, including missing information such as safety in patients over 75 years of age. In addition, a revised study protocol for the planned patient registry should be submitted to national competent authorities before re-launch of the product. The protocol should include a statistical analysis plan and data collection form. Other comments provided to the MAHs are also to be taken into account, such as that the descriptive statistic should include comparative analysis, off label use should be assessed as part of the missing information, and all tables should be completed appropriately. Furthermore, a restricted distribution of aprotinin should be envisaged with aprotinin available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry. The MAHs of aprotinin containing medicinal products are encouraged to work together towards the institution of a single registry.

The CHMP, having considered the data submitted was of the opinion that the MAHs for aprotinin containing medicinal products should submit a direct healthcare professional communication. This is considered an additional risk minimisation activity (see section 2.5 Communication plan). The effectiveness of this measure will also be evaluated through periodic reports of data from the proposed registry which will summarise compliance.

2.4. Overall benefit/risk assessment

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 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 recommended 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.

2.5. Communication plan

As part of this referral procedure, the MAH for medicinal products containing aprotinin and the CHMP agreed the wording of a 'Direct healthcare professional' communication (DHPC) designed to inform prescribers of the lifting of the suspension for aprotinin and highlighting the safety concerns with this medicinal product. The letter is to be distributed after the adoption of the Commission Decision. The key messages have been agreed and each member state will ensure that the relevant information is included in the translation in their national language, as applicable.

2.6. Changes to the product information

The CHMP considered all available evidence and recommended a harmonisation of the product information for all products affected by this review. The CHMP recommended the lifting of the suspension for aprotinin, therefore a review of the content of the clinical part of the product information was undertaken to ensure that all safety concerns are captured and that the most up to date safety information is reflected for healthcare professionals and patients.

Aprotinin
The main changes to the summary of product characteristics (SPC) were sections 4.1 (use in adults patients at high risk of major blood loss; clarification of isolated CABG surgery and reference to benefit risk consideration); 4.4 (inclusion of warnings on mortality and risks associated with under-heparinisation); and 4.8 (inclusion of wording on mortality). Other clinical sections were revised for consistency with the wording included and to bring the sections in line with the quality review of documents templates. The package leaflet (PL) was updated accordingly with the changes proposed to the SPC.

The CHMP considered that the indication for aprotinin should read:

'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).'

For other detailed changes, please refer to the final approved SPC/PL attached to the Opinion.

2.7. Re-examination procedure

Following the CHMP conclusion and recommendations for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, one MAH submitted detailed grounds for the re-examination of the CHMP opinion. The re-examination was on tranexamic acid, and for more details please refer to the opinion and assessment report on tranexamic acid.

3. Overall conclusion on aprotinin

Having considered the overall data provided by the MAHs in writing and at the oral explanation, data available from literature reviews and the outcome of a scientific advisory group, the CHMP concluded that

For aprotinin

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 analysis 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 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 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 to the terms 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.

The divergent positions are annexed to this report and appended to the Opinion.

Annex

Divergent positions

Article 31 referral of Directive 2001/83/EC

Procedure No: EMEA/H/A-31/1267

Antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid

Divergent statement

The CHMP delegates express hereby their divergent views with regards to the opinion given by the CHMP within the Article 31 procedure for the lifting of the suspension of marketing authorisations (MA) for products containing aprotinin. The reasons for the divergent views are summarized as follows:

Several data sources point towards an increased risk of mortality and morbidity with aprotinin, relative to comparators. The MAH's database of all placebo-controlled CABG trials suggested a non-significantly increased risk of in-hospital mortality (OR 1.09, 95% CI: (0.78, 1.52)) with aprotinin, with increased mortality risk mostly driven by repeat-CABG studies. Furthermore, an association between aprotinin use and increased mortality was reported in some nonrandomised observational studies (eg, Mangano 2007, Schneeweiss 2008, Olenchock 2008, Shaw 2008) but not others (eg, Karkouti 2006, Mangano 2006, Coleman 2007, Pagano 2008, Ngaage 2008, Karkouti, 2009). Whilst observational studies may always be subject to some biases and confounding, we believe that the available data raise an important signal. Furthermore, an interim analysis of the randomised BART study found an increased risk of all-cause mortality with aprotinin relative to EACA and TXA which led to suspension of the MAs for aprotinin. Given that that BART demonstrated a decrease in massive post-operative bleeding compared to both TXA and EACA, a mortality advantage might have been expected; and therefore the results are particularly worrying.

The MAH's criticisms of the BART study, in particular relating to the apparent under-heparinisation of patients given aprotinin compared with EACA or TXA are not accepted, as the data on heparinisation and mortality across all the study sites do not fully fit with this hypothesis. Lack of information on exact dosing, intraoperative ACT values and outcome in each patient, make it impossible to draw conclusions about any link between heparinisation and mortality in BART. Post-Hoc analyses such as these, (and similarly, on the low use of aspirin in BART suggesting a low-risk and therefore inappropriate study population), can only be used to speculate on the possible causes rather than providing firm supporting evidence. While there is uncertainty over the underlying reason and mechanisms, appropriate risk minimisation is impossible to plan effectively.

The totality of the available data do not firmly establish nor refute an association between aprotinin use and increased mortality, however, a real increase in mortality remains a likely explanation for the BART findings given the differing methodologies, strengths and limitations of the numerous studies in this area. Although findings across studies were not consistent they tend to provide more reasons for concern than reassurance. While such uncertainty remains over the risk of mortality associated with use of aprotinin, the precautionary principle should operate, such that a change in the regulatory position should only take place in the face of clear evidence of no increased risk of mortality associated with aprotinin. Such a position has not been reached.

Further information on the benefit/risk balance should therefore be obtained before the product can be returned to the market, and the only source of information sufficiently robust to address the current uncertainties would be a large randomised control trial. The MAH considers such a trial is unfeasible and thus this question cannot be addressed; in this scenario a lifting of the suspensions of MA should not be considered.

CHMP members expressing a divergent opinion:

Andrea Laslop (AT)	30 May 2013	Signature: .....
Pierre Demolis (FR)	30 May 2013	Signature: .....
Barbara van Zwieten-Boot (NL)	30 May 2013	Signature: .....
Bruno Sepodes (PT)	30 May 2013	Signature: .....
Jan Mazag (SK)	30 May 2013	Signature: .....
Concepcion Prieto Yerro (ES)	30 May 2013	Signature: .....
Ian Hudson (UK)	30 May 2013	Signature: .....
Hubert Leufkens (co-opted)	30 May 2013	Signature: .....
Robert Hemmings (co-opted)	30 May 2013	Signature: .....
Sol Ruiz (co-opted)	30 May 2013	Signature: .....