LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Trasylol
(aprotinin)

SE/H/1671/01/MR

This module reflects the scientific discussion for the approval of Trasylol. The procedure was finalised on 2018-02-06. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Nordic Group BV has applied for a marketing authorisation for Trasylol, solution for injection/infusion, 10000 KIU/ml. The active substance is aprotinin, bovine (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.).

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Considering the long clinical experience of the product there is sufficient clinical experience to establish most aspects of clinical efficacy and safety. Regarding mutagenic potential and reproductive toxicity, further information is given below.

Reproduction toxicity
In rat intravenous studies, daily doses of up to 80,000 KIU/kg produced no maternal toxicity, embryotoxicity, or foetotoxicity. Daily doses of up to 100,000 KIU/kg did not interfere with the growth and development of the young and doses of 200,000 KIU/kg/day were not teratogenic. In rabbits, daily intravenous doses of 100,000 KIU/kg produced no evidence of maternal toxicity, embryotoxicity, foetotoxicity or teratogenicity.

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

Environmental Risk Assessment
The drug product is a protein derived from bovine lung. Thus, aprotinin is unlikely to result in a significant risk to the environment.

IV. CLINICAL ASPECTS

Trasylol (aprotinin) was approved for the first time in the world in Germany in 1959 (IBD) as treatment for conditions associated with excessive bleeding. A national marketing authorisation was granted in Sweden in 1967.

According to the MAH, the global cumulative patient exposure has been estimated to 3,332,000 patients for the period 01 January 1984 to 28 February 2016.

IV.1 Pharmacokinetics
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 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 131I-aprotinin healthy volunteers excreted within 48 hours 25 - 40 % of the labelled substance as metabolites in the urine. These metabolites lacked enzyme-inhibitory activity.

IV.2 Pharmacodynamics
Aprotinin act as inhibitor of multiple mediators (e.g. kallikrein, plasmin, trypsin) resulting in attenuation of inflammatory responses, fibrinolysis and thrombin generation.

IV.3 Clinical efficacy
Aprotinin was first approved in 1959 and the information provided by that time is considered obsolete. The assessment of clinical efficacy is therefore based on a later review.

Summary of the BART study
In the BART trial (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), the efficacy of aprotinin was compared with tranexamic acid and with aminocaproic acid in cardiac surgery.
The primary objective of the trial was “to definitively determine if aprotinin is superior to

epsilon-aminocaproic acid and tranexamic acid in terms of massive postoperative bleeding in the initial 24-hours following surgery." The secondary objective was "to determine if aprotinin is comparable or superior to epsilon-aminocaproic acid and tranexamic acid in terms of: (i) allogeneic exposure to any blood product and (ii) decreasing fatal/life-threatening and serious postoperative complications in the 30-day perioperative period."

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:

- 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 defined as one or more of the following commencing within the first 24 hours following protamine administration:

- Bleeding from chest tubes exceeding 1.5 L over an 8-hour period
- Replacement of blood exceeding 10 RBC units over 24 hours
- Death due to hemorrhage
- Re-operation for hemorrhage and tamponade.

The protocol-specified secondary outcomes were

- Allogeneic exposure to any blood product
- Fatal/life-threatening event, defined as one or more of the following:
- 30-day all-cause mortality
- myocardial infarction
- cerebrovascular accidents (focal neurologic deficit lasting more than 24 hours)
- Serious adverse event, defined as one or more of the following:
- Dialysis-dependent renal failure
- Need for prolonged invasive mechanical ventilatory support (greater than 48 hours)
- Prolonged low output state (need for vasopressors, balloon pump, or ventricular assist device for more than 48 hours).

Two interim analyses were planned in the protocol, and carried out in December 2004 (N= 970 patients) and January 2007 (N=1896 patients).
In October 2007, the BART Data Safety Monitoring Board (DSMB), after reviewing preliminary data on 2163 patients, recommended that patient entry into the aprotinin treatment group be stopped. The reason given for this recommendation was a higher number of deaths in the aprotinin group that had "almost reached conventional statistical significance for 30-day mortality compared to Drug B (relative risk 1.5; P=0.06) and Drug C (relative risk 1.5; P=0.08)".

Summary of the efficacy results in BART study
Error! Reference source not found. and Table 1 show the results from the original publication of Fergusson et al from May 2008 in NEJM.

Table 1 Paired Comparisons for the Primary Outcome, Massive post-operative bleeding

	Aprotinin vs. Tranexamic Acid			Aprotinin vs. Aminocaproic Acid		
	p	**Relative Risk (95% CI)**	**Absolute risk (%)**	**p**	**Relative Risk (95% CI)**	**Absolute risk (%)**
Re-operation for bleeding Fergusson publication (N=2330)	0.10	0.79 (0.59, 1.05)	9.5 vs 12.1	0.10	0.79 (0.59, 1.05)	9.5 vs 12.1
Bleeding from chest tubes						
Fergusson publication (N=2330)	0.07	0.70.	5.3 vs 7.5	0.02	0.63	5.3 vs. 7.5

Table 1 Paired Comparisons for Components of the Primary Outcome, Re-operation for bleeding, and Bleeding from chest tubes as reported in the Fergusson publication (N=2330)

	Aprotinin vs. Tranexamic Acid			Aprotinin vs. Aminocaproic Acid		
	p	**Relative Risk (95% CI)**	**Absolute risk (%)**	**p**	**Relative Risk (95% CI)**	**Absolute risk (%)**
Re-operation for bleeding Fergusson publication (N=2330)	0.05	0.68	5.5 vs 8.1	0.04	0.67	5.5 vs 8.2
Bleeding from chest tubes						
Fergusson publication (N=2330)	0.07	0.70.	5.3 vs 7.5	0.02	0.63	5.3 vs. 7.5

Efficacy in other randomised trials and observational studies

The following tables present a summary of the available data on the efficacy of aprotinin. The

primary CABG trials are summarised in Table 2 and the trials in repeat CABG surgery in Table 3.

Table 2 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.

Table 3 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 (Table 4) and in repeat CABG (Table 5).

Table 4 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.

Table 5 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.

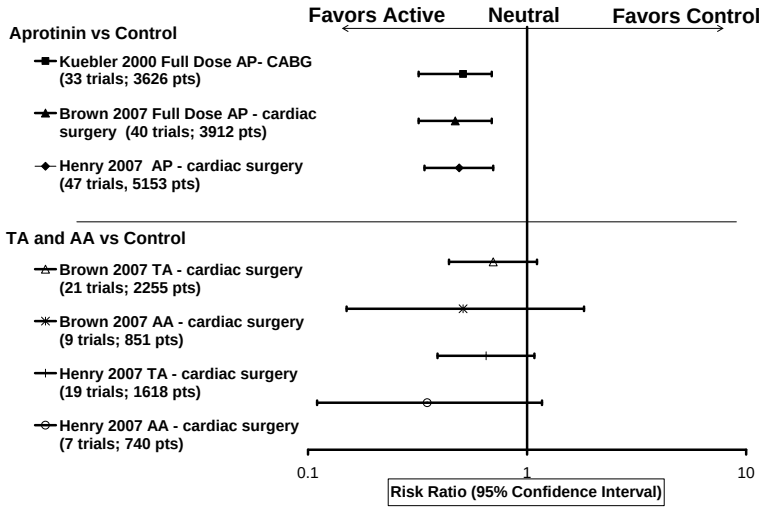
Results from a recent review (Henry et al) indicate that in cardiac surgery aprotinin reduced the need for re-operation due to bleeding compared to placebo or no treatment by a relative 54% (RR 0.46; 95% CI 0.34-0.63) and exposure to allogeneic blood by a relative 32% (RR 0.68; 95% CI 0.63-0.73). According 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., 1996, n=6015] from 3.3% to 9.5% [Dacey L.J. et al., 2000, n=8586], and from 5.5% to 22% [Unsworth-White, M.J., et al., 1995, 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.

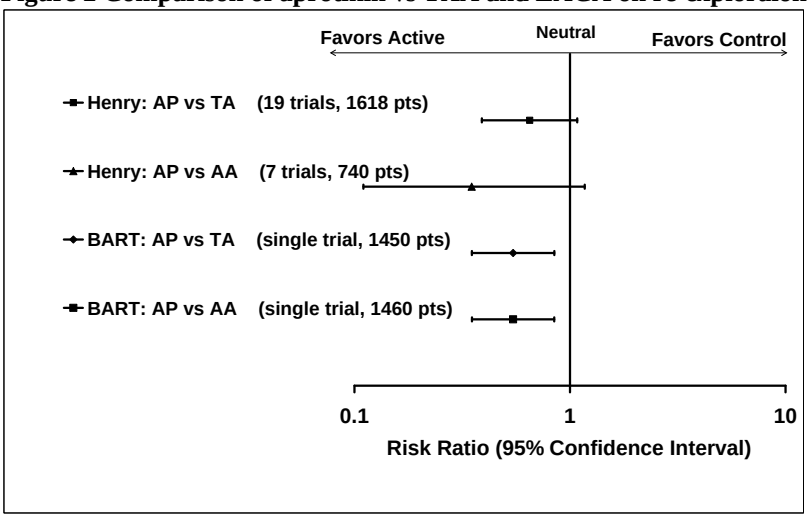
Figure 1indicates that in the meta-analyses shown, aprotinin significantly reduced the risk for re-exploration compared to the control group, a randomised group other than aprotinin, tranexamic acid or aminocaproic acid, generally placebo. In contrast, a significant reduction in the re-operation rate was not observed for tranexamic acid and aminocaproic acid in comparison to their respective control groups.

Figure 1 Risk of re-exploration due to bleeding in three meta-analyses



The biggest meta-analysis referred in Figure 1 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 Figure 2 below there was a trend favouring aprotinin with respect to the need for re-operation for bleeding.

Figure 2 Comparison of aprotinin vs TXA and EACA on re-exploraion



In summary, 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.

The efficacy results observed in the BART study were consistent with results from other randomised clinical studies and observational studies.

IV.4 Clinical safety

The scientific grounds for initial approval of aprotinin in 1959 are considered obsolete. The assessment of clinical safety is therefore based on more recent reviews.

Summary of the safety results in BART study

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 below.

Table 6 30-day all-cause mortality, including all randomised subjects for whom data was available, in BART study

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 7** below).

Table 7 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).

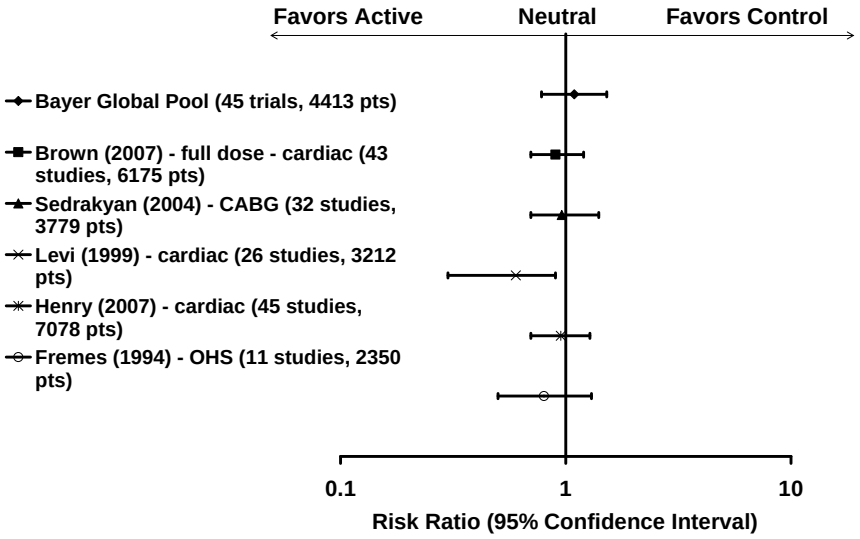
The impact of aprotinin in the reduction of massive bleeding is considered of clinical relevance. Although the link between blood loss and mortality has not been proven, bleeding less would result in fewer complications, fewer transfusions and less time spent in hospital, which was considered clinically relevant.
Regarding heparinisation, the 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.

Safety in other randomised trials and observational studies
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. Figure 3 below summarises the results from meta-analysis of randomised studies comparing aprotinin with placebo or no treatment.

Figure 3 Perioperative mortality risk as estimated in meta-analyses



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 re-analysed data of Mangano et al (2006), 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 studies by Karkouti et al (2006; 2009), 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 tables below summarise the results from observational studies (perioperative [Table 8] and long-term mortality [Table 9]).

Table 8 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	Aprotinin 3,481	Unknown	Unknown	1.03 (0.71-1.49)[c]

(Cardiac surgery 1998-2006)	No Aprotinin 4,355			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.

Table 9 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%).

Table 10 Spontaneous reports of adverse events classified by MedDRA 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%)

Risk minimisation measures applied

- A clarification is 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.

- A registry is conducted by MAHs of aprotinin containing medicinal products affected by this review. The registry monitors 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 collected.

- The product information's clinical parts were revised 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 was also defined.

IV.5 Risk Management Plan

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Losibere 2 mg/125 mg tablets, Procedure number: NL/H/2730/001. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The scientific grounds and benefit/risk discussion from the initial approval of aprotinin in 1959 were considered obsolete. The assessment of benefit/risk is therefore based on a later review.

Benefits

In terms of efficacy, randomised clinical studies' results 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 due to 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 and 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. 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.

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.

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 was concluded 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 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, it is considered that

there is clear evidence of a patient population in which the efficacy of systemic aprotinin clearly outweighs its risks.

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.

Summary of benefit/risk ratio

The benefit/risk ratio for Trasylol (aprotinin) is considered positive for adult patients who are at 'high-risk' of major blood loss undergoing cardiopulmonary bypass in the course of 'isolated CABG' surgery.

The MAH has committed to a category 1 post-authorisation safety study (PASS) "Nordic Aprotinin Patient Registry", in which the MAH is obligated to collect data for a minimum of 3 years.
Aprotinin can only be made available to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to enrol in the Aprotinin patient registry.

No new and significant safety findings were identified from the peer-reviewed scientific literature or clinical studies in the reporting period of the latest PSUSA (PSUSA/00000230/201602). It was concluded, that based on the data presented, the benefit-risk balance of aprotinin remains unchanged as per the licensed indication. However, no patient was exposed to Trasylol during the reporting interval since the sales volume is nill.

The benefit/risk ratio is therefore considered positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

Description	**Due date**
Category 1 PASS: The Trasylol Patient Registry in Europe	Study start: Since the day that Trasylol becomes available to the market. Study completion: Following accrual of three years data Final report: Within one year of completion of study

VII. APPROVAL

The Mutual recognition procedure for Trasylol, solution for injection/infusion, 10000 KIU/ml was positively finalised on 2018-02-06.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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