Pharmacology / Toxicology Review Memorandum - ARTISS

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Pharmacology / Toxicology Review Memorandum
Date: February 26, 2008 (Final review memo)
From: Paul W. Buehler
Through: Abdu Alayash, Susan Abbondanzo and Basil Golding
To: Pratibha Rana and Tim Lee
Subject: STN-125266 Fibrin Sealant (FS VH S/D 4, frozen and lyophilized) for adhering autologous skin grafts to surgically prepared wound beds resulting from burns in adults and pediatric populations.
Sponsor: Baxter Healthcare
Receipt Date: June 1, 2007
Middle Cycle/Final Review: November 1, 2007

Recommendation:
STN 125266-0 is approvable from a pharmacology and toxicology perspective. Primary toxicology was carried out in submission # STN 103980/5224 which supported approval of TISSEEL VH S/D with synthetic aprotinin at thrombin concentrations 125x the concentration present in the FS VH S/D 4 product. Otherwise the TISSEEL VH S/D and FS VH S/D 4 are no different in terms of chemical composition. It is not believed that reduction in thrombin present in the FS VH S/D 4 product would lead to toxicology not associated with TISSEEL VH S/D (see appendix for studies and review of studies submitted with STN 103980/5224).
Indication:
Fibrin Sealant, VH S/D 4 (frozen and lyophilized) is indicated to adhere to autologous skin grafts and surgically prepared wound beds resulting from burns in adult and pediatric populations. The product is supplied as a lyophilized powder to be reconstituted as 2 mL (100 cm^2), 4mL (200 cm^2) and 10 mL (500 cm^2) volumes, depending on surface area to be covered.
Background:
On 27 July 2006, FDA approved eBLA supplement (STN: BL 103980/5121) supporting licensure of Baxter's next generation Fibrin Sealant, "TISSEEL VH S/D". Fibrin Sealant, Vapor Heated, Solvent/Detergent Treated (TISSEEL VH S/D) is a further development of TISSEEL VH Fibrin Sealant. Viral inactivation steps are included in the manufacturing process of both TISSEEL VH Fibrin Sealant and TISSEEL VH S/D to address the potential for transmission of viral pathogens. Solvent/detergent treatment of both biological components of TISSEEL VH S/D, specifically Sealer Protein Concentrate

(Human) and Thrombin (Human) provides an increased margin of safety relative to TISSEEL VH Fibrin Sealant. On 26 February 2007, FDA approved the PAS (STN: BL 103980/5224) supporting replacement of the bovine aprotinin with equivalent synthetically derived aprotinin supplied by --------- (see appendix).

Fibrin Sealant VH S/D 4 is a parallel development to TISSEEL Fibrin Sealant (BL 103980). Except for the difference in thrombin concentration (4 IU/ml vs. 500 IU/ml), the manufacturing process for ***Fibrin Sealant VH S/D 4*** ----------. The process includes stringent plasma collection and screening processes, as well as two distinct viral inactivation steps that are included in the manufacturing process of both biological components to address the potential for transmission of viral pathogens, heat treatment and solvent/detergent treatment. The concentration of thrombin directly influences coagulation properties. Rapid hemostasis and sealing can be achieved with high amounts of thrombin (TISSEEL) resulting in virtually immediate clot formation. For this reason, thrombin concentrations of 500 IU/ml are usually used for surgical procedures were hemostasis and sealing have to be as fast as possible. However, in situations when time for additional handling is needed after applying the sealant, low thrombin concentrations (e.g 4 IU/ml) are of considerable advantage. Due to the prolonged clotting time, sealants containing low amounts of thrombin are used as biological tissue glues for procedures such as skin grafting. The present file contains one primary non-clinical study evaluating both efficacy and toxicity of ***Fibrin Sealant VH S/D 4*** in a pig model of skin grafting.

The compositions of the two biologic components of ***FS VH S/D 4*** (frozen and lyophilized) and ***TISSEEL VH S/D***, are summarized below:

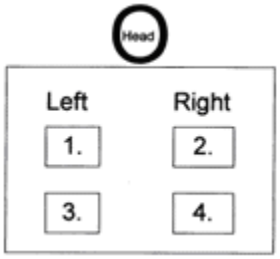
[ ]

Non-clinical studies:

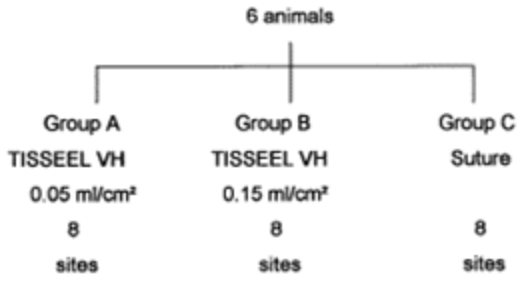
PV 0270102 Sealing of autologous skin grafts in a pig model

Objective: to evaluate/compare wound repair with ***Fibrin Sealant VH S/D 4*** at two different dosages with conventional sutures or spray fibrin sealant (TISSEEL VH) in pigs with a full thickness skin grafts.

Methods: 24 test sites were randomly distributed among 6 animals at 4 site locations on the backs of animals as follows in the diagram below:



Four full skin thickness defects (4x8 cm), the defects were covered with autologous split skin grafts using fibrin sealant or sutures.



Primary end points:

- Seroma and hematoma formation at 7 days
- Take rate at 7 and 14 days
- Assessment of wound area healed at 21 days

Secondary endpoints:

- Ease of application and time for grafting
- Local tolerance histopathology

Scoring/statistics: For comparisons between groups the primary end-points were combined into a rank sum score per site. For this purpose all variables were ranked over treatment groups. For seroma and hematoma formation at 7, 14 and 21 days, lower values received higher ranks. The rank was added up over all variables and the means. A higher rank sum score indicates a better performance.

Results

Differences in primary endpoints:

		0.05 ml/cm² TISSEEL VH	0.15 ml/cm² TISSEEL VH	Suture
Seroma formation at 7 days (% of total wound area)	Median 95% CI Min Max	0.0 0.0 to 0.0 0.0 0.0	0.0 0.0 to 2.5 0.0 2.5	0.0 0.0 to 31.4 0.0 31.4
Hematoma formation at 7 days (% of total wound area)	Median 95% CI Min Max	3.6 0.0 to 15.2 0.0 15.2	0.0 0.0 to 24.1 0.0 24.1	10.7 0.0 to 100.0 0.0 100.0
Take rate at 7 days (% of total wound area with fixed graft)	Median 95% CI Min Max	91.9 82.2 to 100.0 64.7 100.0	96.0 86.1 to 100.0 71.2 100.0	69.9 59.5 to 94.7 0.0 94.7
Take rate at 14 Days (% of total wound area with fixed graft)	Median 95% CI Min Max	99.3 96.7 to 100.0 78.2 100.0	100.0 100.0 to 100.0 90.7 100.0	87.8 80.9 to 100.0 47.9 100.0
Assessment of wound area healed at day 21 (% of total wound area with viable skin)	Median 95% CI Min Max	100.0 94.8 to 100.0 93.1 100.0	100.0 97.0 to 100.0 95.1 100.0	93.4 86.4 to 100.0 66.1 100.0

Differences in secondary endpoints:

		0.05 ml/cm² TISSEEL VH	0.15 ml/cm² TISSEEL VH	Suture
Ease of Application (%)	Low	0.0	0.0	62.5
	95% CI	0.0 to 32.4	0.0 to 32.4	30.6 to 86.3
	Middle	0.0	25.0	37.5
	95% CI	0.0 to 32.4	7.1 to 59.1	13.7 to 69.4
	Best	100.0	75.0	0.0
	95% CI	67.6 to 100.0	40.9 to 92.9	0.0 to 32.4
Time for grafting (Min)	Median	2.4	3.6	13.2
	95% CI	2.0 to 3.5	2.6 to 6.0	11.2 to 18.2
	Min	1.8	1.1	10.5
	Max	3.5	6.0	18.2

Healed wound area at 21 days:

Group A

Animal cons.no./Field	Size (cm²)
1/2	33.48
	33.58
	33.91
2/4	34.25
	34.82
	34.15
4/1	34.74
	34.70
	34.70
5/4	28.47
	28.74
	28.65
6/1	42.75
	42.65
	42.48
6/3	39.83
	40.13
	40.12
7/1	43.59
	43.84
	34.83
7/2	47.30
	47.05
	47.09

Group B

Animal cons.no./Field	Size (cm²)
1/4	37.17
	36.80
	37.14
2/2	41.32
	41.70
	41.41
3/1	35.31
	34.99
	35.27
3/2	39.38
	38.90
	39.00
3/4	35.27
	34.88
	34.38
4/3	33.49
	33.69
	33.39
4/4	27.24
	27.32
	27.28
5/1	32.81
	32.98
	32.72

Group C

Animal cons.no./Field	Size (cm²)
1/1	29.44
	28.93
	28.97
2/1	38.87
	38.32
	39.05
2/3	24.61
	25.02
	25.47
3/3	23.56
	24.09
	23.91
6/2	30.46
	30.68
	30.87
6/4	38.62
	38.79
	38.53
7/3	30.73
	30.71
	30.84
7/4	18.53
	19.13
	19.11

Local tolerance histological findings:
There were no differences between groups in terms of local histology findings at 14 days with most groups demonstrating no (score =0) or low (score=1) for foreign body reaction and residual fibrin. Inflammation was higher across groups with typical scoring of medium (score=2).

Conclusion:

The present study suggests that a fibrin sealant at low concentrations can improve split skin graft fixation compared to standard suturing techniques. No differences between higher and lower dose thrombin were detected in terms of efficacy or local histopathology.

Appendix (STN-103980/5224)

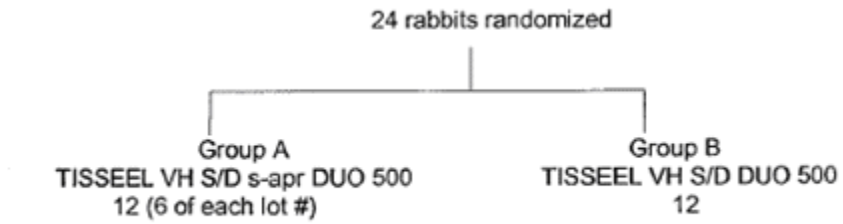
Overview of the Non-clinical Testing Strategy:

Study report (ARC-UL-0791) - "Synthetic Aprotinin": Salmonella Typhimurium reverse mutation test

Study report (PV0890301) - Pharmacokinetics of synthetic aprotinin after intravenous administration in mice

Study report (0910301) - Synthetic aprotinin: Bronchospastic activity in guinea pigs

Study report (1150302) - A comparative evaluation of the sustained hemostatic effacacies of TISSEEL VH S/D s-apr DUO 500 versus TISSEEL VH S/D DUO 500 in a Rabbit liver resection model with acute hyperfibrinolysis
Study report (PV0920301) - Determination of acute toxicity in mice after intravenous administration of synthetic aprotinin
Study report (PV1240402) - Evaluation of the acute toxicity of tisseel VH S/D s-apr Duo 500 versus TISSEEL VH S/D DUO 500 in a rat model
Study report (PV0960301) - Investigation of local tolerance of synthetic aprotinin in rabbits
Study report (PV1280402) - A comparative evaluation of the local tissue reaction of TISSEEL VH S/D s-apr DUO 500 versus TISSEEL VH S/D Duo 500 in a wound healing model (rat)
Study report (PV0940301) - Synthetic aprotinin: skin sensitization study
Pharmacology (efficacy):
Study report (1150302) - A comparative evaluation of the sustained hemostatic effacacies of TISSEEL VH S/D s-apr DUO 500 versus TISSEEL VH S/D DUO 500 in a Rabbit liver resection model with acute hyperfibrinolysis
s-apr = synthetic aprotinin, bv-apr = bovine aprotinin
Summary:
Study 1150302 represents the pivotal "efficacy" study in the evaluation of s-apr in vivo potency comparability to bv-apr in accordance with 21 CFR § 600.3 (potency definition).
Materials evaluated
Test Item - *(TISSEEL VH S/D s-apr DUO 500)*
[ ]
Reference Item - *(TISSEEL VH S/D DUO 500)*
[ ]
Model Rationale/Relevance:
The liver resection model in the rabbit is a reasonable and appropriate model of bleeding for the evaluation of s-apr versus bv-apr for the following reasons: (1) the model represents the type of bleeding for which TISSEEL VH is indicated (i.e. microvascular non-arterial bleeding) and (2) the liver has low intrinsic fibrinolytic potential thus reducing variability.
Study Design:
Under anesthesia (Ketamine/Xylazine maintained with thiopental) 24 animals were heparinized with 4.000 IU/kg. The left liver lobe was resected and control of bleeding was attempted by either test or reference material using a DUPOLJECT applicator (clinically intended method of application). Animals were randomized after liver resection and investigators were blinded to test or reference material.



Twenty minutes after liver resection streptokinase was administered as a bolus injection of 20,000 IU followed by continuous infusion of 40,000 IU over one hour. Blood loss at the sealed surface was quantified for two hours after sealing.
The primary end points were:
1) Blood loss (g) over the first hour after streptokinase administration
2) Blood loss (g) over the second hour after streptokinase administration
3) Total blood loss (g) over the first and second hour after streptokinase administration
Statistical analysis was summarized by median values, 95% confidence intervals of the medians and quartiles (Q1 = 25th, Q2 =50th and Q3 = 75th percentiles) for study arms A and B.

Results:

There was a slight non-significant increase (P>0.05) in blood loss over the first hour and for the combined 2 hour bleeding time evaluations with s-apr versus bv-apr.

Time		Blood loss	
		TISSEEL VH S/D s-apr DUO 500	TISSEEL VH S/D DUO 500
1h	Median	1.8	1.3
	95% CI	1.0 to 2.4	0.9 to 1.8
	Q1	1.1	1.0
	Q3	2.3	1.8
2h	Median	1.0	1.0
	95% CI	0.6 to 2.7	0.7 to 2.5
	Q1	0.7	0.7
	Q3	2.4	2.1
Total	Median	3.1	2.4
	95% CI	1.7 to 4.7	1.7 to 3.8
	Q1	1.9	1.8
	Q3	4.5	3.7

Blood loss per animal over the initial hour, second hour and total time of evaluation

TISSEEL VH S/D s-apr DUO 500

	Bloodloss (g)		
Animal no.	1h	2h	total
1	3.1	0.8	3.9
3	2.0	2.7	4.7
5	1.0	1.0	2.0
6	1.5	2.0	3.5
8	3.2	2.9	6.1
10	1.0	0.7	1.7
12	1.1	0.3	1.4
14	2.2	2.0	4.2
19	2.2	3.2	5.4
20	2.4	0.2	2.6
21	0.7	0.6	1.3
21	1.1	0.9	2.0

TISSEEL VH S/D DUO 500

	Bloodloss (g)		
Animal no.	1h	2h	total
2	1.2	0.5	1.7
4	1.3	3.9	5.2
7	1.5	0.7	2.2
9	0.5	0.2	0.7
11	2.5	1.3	3.8
13	1.0	2.5	3.5
15	0.7	0.7	1.4
16	2.7	2.6	5.2
17	1.8	1.7	3.5
18	1.7	0.7	2.4
22	0.9	0.9	1.8
23	1.3	1.0	2.3

Conclusion:

Based on the Baxter's and this reviewers statistical analysis no statistically significant differences occurred in bleeding time when comparing s-apr versus bv-apr in the rabbit liver resection model of bleeding. The slight trend toward increased bleeding in thes-apr treated group is approximately 0.37 (g) across animals over the initial hour and approximately 0.42 (g) across animals over the total time of evaluation. These

differences are unlikely to show a clinically different response to s-apr versus bv-apr in TISSEEL VH.

Pharmacokinetics/Toxicokinetics:

Study report (PV0890301) - Pharmacokinetics of synthetic aprotinin after intravenous administration in mice

Summary: The study was performed to test and compare the pharmacokinetic (PK) handling of s-apr versus bv-apr following single i.v. dosing. Based on AUC, total body clearance, MRTi..v. and t1/2 there appears to be no differences in the overall PK of s-apr versus bv-apr in the mouse.

Material evaluated

[ ]

Model Rationale/Relevance:

No rationale is provided for use of the mouse as a human PK relevant species. Nonetheless the mouse is adequate based on the idea of comparative PK for "equivalent" products (s-apr versus bv-apr).

Study design:

Six animals per group/time point were randomized to receive (A) s-apr (lot1), (B) s-apr (lot2), (C) bv-apr (lot1) or (D) bv-apr (lot2). All animals were dose with 500,000 KIU/kg (in 20 mL/kg). At 0, 5, 15, 60, 120 minutes and 6 hours post i.v administration 6 animals per group/time point were exsanguinated by cardiac puncture. Serum sample were evaluated by an ---------- method for the determination of aprotinin.

Results:

Actual Doses (ug/kg) Received:

Item Lot No.	Actual dose µg/kg	AUC µg/mL*h	CLs mL/h/kg	MRT hours	t ½ hours
Synth. aprotinin 0549100	69360	179	388	1.27	0.88
Synth. aprotinin 0555440	70100	164	428	1.18	0.82
Bov. aprotinin BXB3D71A	79920	211	378	1.19	0.83
Bov. aprotinin BXB3ZZ1	92840	197	470	1.09	0.75

Overall PK Parameters:

Item Lot No.	Actual dose µg/kg	AUC µg/mL*h	CLs mL/h/kg	MRT hours	t ½ hours
Synth. aprotinin 0549100	69360	179	388	1.27	0.88
Synth. aprotinin 0555440	70100	164	428	1.18	0.82
Bov. aprotinin BXB3D71A	79920	211	378	1.19	0.83
Bov. aprotinin BXB3ZZ1	92840	197	470	1.09	0.75

PK Parameters per Lot:

Test item	Lot Number	Parameter	Unit	Estimate	95% CI for estimate
Synthetic aprotinin	0549100	AUC 0-infinity	µg/mL*h	179	153 to 213
		$t_{1/2}$	hours	0.88	0.80 to 0.97
		CLs	mL/h/kg	388	325 to 452
		MRT	hours	1.27	1.15 to 1.40
	0555440	AUC 0-infinity	µg/mL*h	164	155 to 173
		$t_{1/2}$	hours	0.82	0.78 to 0.87
		CLs	mL/h/kg	428	406 to 453
		MRT	hours	1.18	1.12 to 1.26
Bovine aprotinin	BXB3D71A	AUC 0-infinity	µg/mL*h	211	194 to 240
		$t_{1/2}$	hours	0.83	0.78 to 0.90
		CLs	mL/h/kg	378	332 to 411
		MRT	hours	1.19	1.13 to 1.30
	BXB3ZZ1	AUC 0-infinity	µg/mL*h	197	188 to 209
		$t_{1/2}$	hours	0.75	0.71 to 0.81
		CLs	mL/h/kg	470	444 to 494
		MRT	hours	1.09	1.03 to 1.17

Conclusion:

The PK study would likely have provided much more reliable comparative data if performed following serial blood collections in the same animal after dosing (n=5 per group). The present study introduces a large degree of variability.

Toxicology Overview:

Single Dose Toxicity:

Study report (PV0920301) - Determination of acute toxicity in mice after intravenous administration of synthetic aprotinin

Summary:

No deaths occurred in any dosing group, clinical sign and symptoms were generally absent and gross pathological findings were insignificant.

Study Design:

Test animals were divided into sixteen groups each with ten animals (5M, 5F) according to the following treatment scheme.

Item (Lot no.)	Targeted dose (KIU/kg)	Nominal value (KIU/ml)	Actual value (KIU/ml)	Solution used (KIU/ml)	Injection volume (ml/kg)	Resulting dose (KIU/kg)
synth. Aprotinin 0549100	100,000	3,000	3,029	3,029	33.3	100,866
	500,000	40,000	41,262	41,262	12.5	515,775
	1,500,000	40,000	41,262	41,262	37.5	1,547,325
synth. Aprotinin 0555440	100,000	3,000	2,741	2,741	33.3	91,275
	500,000	40,000	39,960	39,960	12.5	499,500
	1,500,000	40,000	39,960	39,960	37.5	1,498,500

Item (Lot no.)	Targeted dose (KIU/kg)	Nominal value (KIU/ml)	Actual value (KIU/ml)	Solution used (KIU/ml)	Injection volume (ml/kg)	Resulting dose (KIU/kg)
bov. Aprotinin BXB3D71A	100,000	3,000	2,915	2,915	33.3	97,070
	500,000		31,620	31,620	15.8	499,596
	1,500,000		31,620	31,620	47.4	1,498,788
bov. Aprotinin BXB3ZZ1	100,000	3,000	2,901	2,901	33.3	96,603
	500,000		31,538	31,538	15.9	501,454
	1,500,000		31,538	31,538	47.6	1,501,209
Formulation buffer 3074410A	-	-	-	-	33.3	-
	-	-	-	-	12.5	-
	-	-	-	-	37.5	-
Isotonic saline	-	-	-	-	37.5	-

synth. aprotinin = test item, bov. aprotinin = active reference item, formulation buffer and istonic saline = negative reference items

Each animal received a single intravenous injection of the assigned test or reference material into the caudal vein at a flow rate of ≤ 2 mL/min. On day 14 all mice were humanely killed with CO_2. The primary endpoint of this study was mortality. Thus only gross necropsy was performed at day 14 with tissue being preserved for histopathology if gross lesions were observed.

Results:

Clinical Symptoms:

No significant findings, other than behavioral depression in all treatment groups with a NOAEL of 100,000 KIU/kg i.v. in mice.

Body masses at low, medium and high doses:

Body masses at medium and high doses of s-apr demonstrated slightly greater weight gain over bv-apr treated animals.

Gross Pathology and Histopathology:

No significant findings

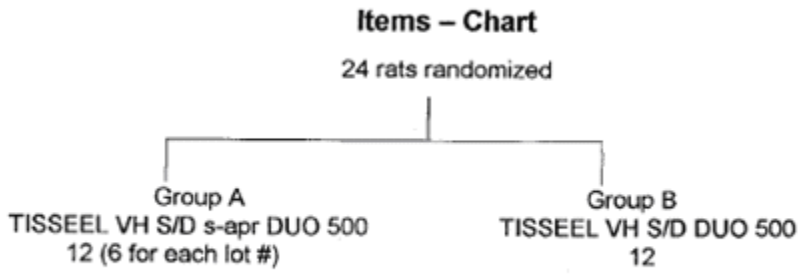
Table VII: Ratio of pathological findings and corresponding 95% confidence intervals for the synthetic aprotinin and the bovine aprotinin.

Item	Dose	Ratio of pathological symptoms (%)	95% Confidence interval for ratio/difference of ratios (%)
Synthetic aprotinin	100,000 KIU/kg	0.0	0.0 to 16.1
	500,000 KIU/kg	5.0	0.9 to 23.6
	1,500,000 KIU/kg	5.0	0.9 to 23.6
Bovine aprotinin	100,000 KIU/kg	0.0	0.0 to 16.1
	500,000 KIU/kg	0.0	0.0 to 16.1
	1,500,000 KIU/kg	5.0	0.9 to 23.6
Difference	100,000 KIU/kg	0.0	-16.1 to 16.1
	500,000 KIU/kg	5.0	-11.6 to 23.6
	1,500,000 KIU/kg	0.0	-19.1 to 19.1

Conclusion: No difference in s-apr versus bv-apr in terms of gross toxicity in mice.

Study report (PV1240402) - Evaluation of the acute toxicity of tisseel VH S/D s-apr Duo 500 versus TISSEEL VH S/D DUO 500 in a rat model

Summary:
No deaths occurred in any dosing group, clinical sign and symptoms were generally absent and gross pathological findings were insignificant. This study was designed to evaluate acute toxicity response to the complete TISSEEL product with either s-apr or bv-apr.
Study Design:
24 rats were randomized to receive the components of TISSEEL with s-apr or bv-apr as follows:



Application/administration of TISSEEL was via the subcutaneous route, this is a technique that has been used successfully in previous animal toxicity studies of in vivo sealant material. Dosing was based on 5 mL/kg of body weight, thus approximating 10x the normal human application. A 40 mL application in an 80 kg individual equals 400 mL or 5 mL/kg bodyweight.
Results:
Body Weights:

TISSEEL VH S/D s-apr DUO 500

male

Animal consecutive no.	Prior to Surgery	Post OP Day 7	Post OP Day 14
2	340	350	410
4	340	370	420
6	350	370	410
8	340	360	380
9	330	370	410
12	350	360	390

female

Animal consecutive no.	Prior to Surgery	Post OP Day 7	Post OP Day 14
13	290	290	290
15	300	320	280
18	260	270	280
19	270	280	280
22	300	300	310
24	300	300	310

TISSEEL VH S/D DUO 500

male

Animal consecutive no.	Prior to Surgery	Post OP Day 7	Post OP Day 14
1	350	360	370
3	350	370	410
5	350	380	400
7	350	390	430
10	340	360	390
11	300	320	330

female

Animal consecutive no.	Prior to Surgery	Post OP Day 7	Post OP Day 14
14	280	290	290
16	290	290	300
17	270	270	320
20	280	280	290
21	320	320	330
23	300	300	320

Gross Pathology and Histopathology:
No significant gross pathology or histopathology was observed
Repeat-Dose Toxicity:
Not performed
Genotoxicity:

Study report (ARC-UL-0791) - "Synthetic Aprotinin": Salmonella Typhimurium reverse mutation test
This is the standard Ames test used to evaluate genetic material alteration required by OECD guidelines. The overall findings indicate that in five strains of bacteria no genetic alterations occurred at the maximum concentration of s-apr or bv-apr that could be applied.

Carcinogenicity:
Not performed

Immunogenicity:
Study report (0910301) - Synthetic aprotinin: Bronchospastic activity in guinea pigs
Summary: The study was performed to test anaphylactoid response to s-apr in a highly sensitive model of acute bronchocspasm. There were no positive anaphylactoid reactions to either s-apr or bv-apr in the guinea pig after rapid i.a. administration.

Material evaluated
[ ]

Model Rationale/Relevance:
The anaphylactoid response in guinea pigs lends itself to critical evaluation of intra-arterial administered induction of histamine with increases in pulmonary filtration pressure. Thus the objective of the study was to study bronchospastic activity of s-apr versus bv-apr under rapid intra-arterial administration.

Study design:
Guinea pigs (n=6/group) were randomized to receive 20,000 KIU/kg s-apr, bv-apr or buffer administered through a carotid catheter. The measured end point was pulmonary infiltration pressure.

Results:
Table 1: Proportion of animals with positive reactions and 95% confidence intervals for the treatment phase.

Item	Positive reactions (%)	95% Confidence Interval for the positive reactions
Synthetic aprotinin	0.0	0.0 to 24.2
Bovine aprotinin	0.0	0.0 to 24.2
Formulation buffer	0.0	0.0 to 39.0
Difference: synthetic aprotinin:bovine aprotinin	0.0	-24.2 to 24.2

Conclusions:
No anaphylactoid or bronchospastic reactions were observed in s-apr, bv-apr or buffer control animals. Thus s-apr does not appear to be any more likely to generate anaphylaxsis in the guinea pig when compared to bv-apr.

Reproductive Studies:
Not performed

Local Tolerance Testing:
Study report (PV0960301) - Investigation of local tolerance of synthetic aprotinin in rabbits
Study report (PV1280402) - A comparative evaluation of the local tissue reaction of TISSEEL VH S/D s-apr DUO 500 versus TISSEEL VH S/D Duo 500 in a wound healing model (rat)

Study report (PV0940301) - Synthetic aprotinin: skin sensitization study
Conclusions from the local tolerance tests suggest no increased risk of local irritation or pathology due to addition of s-apr versus bv-apr.

Reviewer Recommendation:

The present submission demonstrates the following in accordance with 21 CFR § 600.3 under (p) safety and (s) potency.

(1) The synthetic form of aprotinin (s-apr) is equally safe compared to bovine source aprotinin (bv-apr) based on non-clinical GLP toxicology evaluation comparing the two head to head.

(2) The synthetic form of aprotinin (s-apr) is equally potent compared to bovine source aprotinin (bv-apr) *in vivo* based on non-clinical GLP comparability studies, which reflect the intended use of the product component.

From a non-clinical Pharmacology-Toxicology perspective the synthetic form of aprotinin is equivalent to bovive source aprotinin and is approvable for use in the TISSEEL end product.

-