European Medicines Agency

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ASSESSMENT REPORT FOR TACHOSIL

International non-proprietary name/Common name:
human fibrinogen / human thrombin

Procedure No. EMEA/H/C/000505/II/0019

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

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1. Introduction

TachoSil (TC-S) is a ready-to-use absorbable medicated sponge, developed for support of haemostasis and tissue sealing. It consists of an equine collagen sponge coated with human Fibrinogen and human Thrombin, which are well-established components of fibrin sealants.

TachoSil was granted a marketing authorisation by the European Commission on 8 June 2004 for *supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient.* Its efficacy and safety have been demonstrated in controlled trials.
The initial marketing authorisation application was based on a clinical development programme where haemostatic efficacy and safety of TC-S was demonstrated in two liver resection studies (TC-014-IN and TC-016-IN). The programme also included one trial in lung lobectomy (TC-013-IN), which failed in the planned analyses to show statistically significant results for air sealing due to the absence of intraoperative air leakage in an unexpected fraction of more than 50% of the included patients. Subsequently, one kidney resection trial (TC-015-IN) was submitted and assessed as part of a variation application (EMEA/H/C/000505/II/0006).

Two studies were performed as post-approval commitments. The first was an observational cohort study (TC-018-IN) to investigate the potential occurrence of post-treatment adverse reactions, specifically thromboembolic and immunological events, and drug interactions leading to thromboembolic events or major postoperative rebleeding. The second trial (TC-019-IN) investigated the efficacy and safety of TC-S in liver surgery on paediatric patients between 4 weeks and 6 years of age. The reports of both studies have been submitted during the current variation application procedure as FUM 011 and FU2 012.3, respectively. Their assessments are ongoing.

With the aim to expand the therapeutic indication of TC-S to include tissue sealing, two additional clinical trials were initiated in lung and cardiovascular surgery, where the intraoperative pathophysiological situation required effective sealing of air or blood leakage. The table below summarises the overall international clinical development programme for TC-S:

Table 1 - List of international clinical trials with TC-S

	Surgical indication	Study code	Treatments	N	Status
1	Lung lobectomy	TC-013-IN	TC-S vs. standard surgery	189	Reported
2	Liver resection	TC-014-IN	TC-S vs. argon beamer	121	Reported
3	Kidney resection	TC-015-IN	TC-S vs. standard surgery	185	Reported
4	Liver resection	TC-016-IN	TC-S vs. argon beamer	119	Reported
5	A range of surgeries	TC-018-IN	TC-S (no comparison)	≦3170	Ongoing/ reporting
6	Liver resection (children)	TC-019-IN	TC-S (no comparison)	16	Ongoing/ reporting
7	Lung lobectomy	TC-021-IM	TC-S vs. standard surgery	301	Reported
8	Cardiovascular surgery	TC-023-IM	TC-S vs. haemostatic fleece	120	Reported

In this application, the Marketing Authorisation Holder (MAH) proposes to extend the indication as follows:

TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis, *to promote tissue sealing, and for suture support in vascular surgery* where standard techniques are insufficient (see SPC section 5.1)".

To support this application, the MAH has completed two additional clinical trials: TC-021-IM (lung study) and TC-023-IM (cardiovascular study). Changes to the indication are proposed in accordance with the Core SPC for Plasma derived Fibrin Sealant/Haemostatic Products (CHMP/BPWG/153/00).

In addition, the MAH proposed to update section 4.4 of the SPC by deleting the warning on the use of TC-S in vascular surgery, having now generated data on the use of TC-S in cardiovascular surgery in Study TC-023-IM. Also, the MAH proposed to update sections 4.8 and 5.1 of the SPC.

2. Clinical aspects

Both studies supporting this variation application were conducted within EU and according to principles of GCP and with adherence to ICH guidelines. In addition, one site in Switzerland participated in Study TC-021-IM, and met the ethical requirements of Directive 2001/20/EC.

2.1 Clinical pharmacology

No new clinical pharmacology data was included in this application.

The MAH considered that the tissue sealing and haemostatic properties of fibrinogen based products cannot be separated due to the gluing and sealing effect of the viscous fibrin clot deposited at the wound site. The haemostatic efficacy of TC-S thus to some extent mirrors the product's tissue sealing properties. This is reflected in the pharmacodynamic properties described in the SPC of TC-S (SPC, section 5.1). The collagen sponge carrier adds further to the haemostatic and tissue sealing effect by holding the fibrin glue components in place at the wound site, thus avoiding dilution by washing-off, and by providing a mechanical barrier to support the sealing. To reiterate some of non-clinical data from the original submission, TC-S showed good tissue sealing and haemostatic efficacy with strong adhesion to the wound surface. Studies with experimentally increased intra-organ pressure are of special relevance and showed good adhesive and sealing properties of TC-S. One non-clinical study showed good haemostatic efficacy of TC-S under hyper-fibrinolytic conditions. A further study tested the adhesive and sealing properties of TC-S in an *ex vivo* artificial lung model, mimicking the application on the visceral pleura of the lung for air sealing. TC-S was shown to withstand an air pressure of approximately 65 hPa, which is in the upper range of physiological airway pressures, e.g. during a strong cough. The above investigations were designed to test the tissue sealing and haemostatic efficacy of TC-S (lacking the anti-fibrinolytic aprotinin) compared to the predecessor product TachoComb H (with aprotinin). There could be a potential interaction with concomitantly used anticoagulants such as heparin. This question has been investigated as part of the post-marketing safety monitoring study (TC-018-IN).

2.2 Clinical efficacy

The clinical evidence in support of this variation was derived from two pivotal trials concerning the tissue sealing efficacy and safety of TC-S. The trials were designed to demonstrate tissue sealing from two different surgical settings. The outcome variables of the lung lobectomy trial (study TC-021-IM) reflect directly the pure tissue sealing properties of TC-S, i.e. intra- and postoperative sealing against alveolar air leakage, while the endpoints of the cardiovascular trial (study TC-023-IM) reflect the ability of TC-S to establish a mechanical barrier against the high pressure of arterial bleeding and induce local haemostasis at the site of application. In addition, the latter trial was intended to generate clinical data to demonstrate the efficacy and safety of TC-S as suture support in vascular surgery.

Table 2 - Study details of pivotal trials for new indications

Study ID	No. of study centres / locations	Design	Study Treatments	Study Objective	Subjs by arm entered/ compl.	Diagnosis Incl. criteria	Primary Endpoint
TC-021-IM	12 sites/ Austria Belgium Denmark Germany Hungary Italy Sweden Switzerland	Open randomized prospective multi-centre parallel-group phase IIIb	TachoSil vs. standard surgical treatment	Sealing efficacy and safety in pulmonary air leakage after lobectomy	301 randomized, 148 TachoSil, 151 control (ITT)	Air leakage grade 1 and 2 after lung lobectomy in subjects with lung malignancy	Duration of post-operative air leakage
TC-023-IM	10 sites/ Denmark France Germany Italy Spain	Open randomized prospective multi-centre parallel-group phase IV	TachoSil vs. any (standard) haemostatic fleece without active coagulation stimulating compounds, i.e. oxidised cellulose, cotton gauze or the like	Efficacy and safety in cardiovascular surgery	120 randomized, 59 TachoSil, 60 control (ITT)	Elective surgery on the heart, ascending aorta or arch, requiring a cardiopulmonary bypass, bleeding from surgical site	Proportion of patients with haemostasis at 3 minutes

It is important to stress that the applicant has already conducted a trial with TC-S in pulmonary lobectomy (TC-013-IN), in which 189 subjects scheduled for lobectomy due to lung cancer were included. The design of TC-013-IN was essentially identical to that of the TC-021-IM trial, except for the following: (i) Subjects with absence of persistent air leakage (Grade 0) following lobectomy and primary stapling were included, and (ii) the primary efficacy endpoint was presence of air leakage 48 hours after surgery. Unexpectedly, about half of the subjects achieved Grade 0 air leakage following the primary stapling, thus eroding the power of the trial. This caused the outcome of the planned analyses of difference in treatment efficacy to be statistically insignificant. The ITT analysis of all subjects in TC-013-IN, regardless of the degree of air leakage at randomisation, showed that air leakage 48 (± 6) hours after surgery (primary efficacy endpoint) was present in 34% for TC-S and 37% for standard treatment (p=0.76). The odds ratio (OR) of presence of air leakage with TC-S compared to standard treatment was 0.91 (95% confidence interval (CI): 0.48 - 1.72). Assessment of secondary endpoints showed no significant differences between treatment groups. However, ITT analyses of the sub-population with persistent air leakage after primary stapling (Grades 1 - 2; n=89) indicated efficacy of TC-S (analyses not pre-defined in protocol).

Based on the findings of this trial, the applicant has decided to conduct a second lung trial, which was to include subjects with air leakage Grade 1 and 2, only.

2.2.1 Study TC-021-IM and Study TC-023-IM

- Methods

Study Participants

In Study TC-021-IM, subjects were eligible for study participation if they had an elective lobectomy for lung malignancy with intrapulmonary lymphadenectomy. They were randomized to TachoSil or standard surgical treatment when intraoperative air leakage had been assessed by water submersion test. Air leakage Grade 1 (mild, countable bubbles) and Grade 2 (moderate, stream of bubbles) qualified for inclusion. Patients with air leakage Grade 3 (severe, coalesced bubbles) could be reassessed by submersion test after further stapling or limited suturing. Patients with no air leakage (Grade 0) were not eligible for inclusion.

In Study TC-023-IM, patients undergoing a planned elective surgery on the heart, the ascending aorta or aortic arch and requiring a cardiopulmonary bypass procedure were included.

Treatments
TachoSil is a sterile, ready-to-use, absorbable sponge for intra-operative topical application. It consists of an equine collagen sponge coated with the fibrin glue components human fibrinogen (5.5 mg/cm^2) and human thrombin (2.0 IU/cm^2). The active side is coloured with riboflavin. The sponge size used in both trials was 9.5 x 4.8 x 0.5 cm and could be cut. The sponge(s) had to cover the site(s) at least 1 – 2 cm beyond the immediate margins. If more than one sponge was used, the individual sponges had to overlap. The sponge(s) should be applied with pressure for 3 min.

Patients randomized to the control group received (additional) standard treatments.
In the lung study these should be sutures, staples or even no treatment according to the routine at the site. Forty-two (28%) of the 150 standard treatment subjects had no additional standard treatment after randomisation. During the first round of trial treatment, suturing was used in 79 subjects (53%), stapler in 23 (15%) and other standard treatment in 4 subjects (3%).

In the cardiovascular study standard haemostatic treatment should be any haemostatic fleece material without additional active coagulation stimulating compounds, applied with pressure for 3 minutes. Twenty-eight (49%) patients in the standard treatment group were treated with compression and gauze, 24 (42%) with compression and fibrillar absorbable haemostatic fleece, 4 (7%) with suture and 1 (2%) with Tissucol®.

Objectives
Study TC-021-IM compared the sealing efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intra-operative pulmonary air leakage after lobectomy in subjects with lung malignancies with or without metastases.
Study TC-023-IM compared the efficacy and safety of TachoSil in cardiovascular surgery to standard treatment of haemorrhage.

Outcomes/endpoints
In study TC-021-IM, the primary efficacy endpoint was the duration of post-operative air leakage following provocation by coughing; secondary efficacy endpoint was the reduction of intra-operative air leakage intensity after the first application of trial treatment. Descriptive variables were the total number of days until removal of the (last) chest drain and predefined post-operative complications (pneumonia, pulmonary embolism, atelectasis of the lung, surgical wound infection, cardiac arrhythmia, progression/increase of soft tissue emphysema documented by X-ray, need for additional chest drainage, need for re-operation, need for respiratory assistance, bleeding and need for blood transfusion).

Primary efficacy endpoint in study TC-023-IM was the proportion of patients achieving haemostasis after 3 minutes and, as secondary efficacy endpoint, haemostasis after 6 minutes. If haemostasis was not achieved after 3 minutes, another piece of trial treatment (TC-S or standard fleece material) was applied for 3 min. If haemostasis was achieved, “time to haemostasis” was recorded as 6 min. If after 6 min, haemostasis was not achieved, rescue treatment could be initiated. Other endpoints were the incidence of re-operation due to bleeding complications, post-operative transfusion, duration and volume of drainage.

Sample size
The calculation of the sample size for Study TC-021-IM was based on experience from previous clinical trias. In study TC-013-IN subjects with intra-operative air leakage grade > 0 had a median duration of post-operative air leakage of 1 day when treated with TachoSil and 2 days when allocated to standard treatment. Based on these data, 10,000 trials were simulated by selecting subjects from the above mentioned subpopulation in TC-013-IN using random sampling with replacement. Equal number of subjects was chosen from each of the two treatment groups and in each trial the log-rank test performed to assess the difference between treatments. The percentage of trials with the log-rank

test showing statistical significance for α = 5% was used as power estimate. Based on these simulations a total sample size of 300 subjects, resulting in a (simulated) power of about 94% was chosen.

For Study TC-023-IM, anticipating a 75% responder rate (i.e. patients with haemostasis after 3 minutes) in the TachoSil group vs. 45% responder in the comparator group, a chi-squared test would require 61 patients per group to detect this difference with 90% power (Type I error: 0.05, 2-sided).

Randomisation
Subjects were randomised to either TachoSil or additional (standard) surgical treatment (TC-021-IM) and standard haemostatic treatment (TC-023-IM) respectively by means of a central Interactive Voice Response System (IVRS). After having received specific user (site) identification, trial identification and age of the subject to be randomised, the IVRS informed the investigator of subject number and the trial treatment allocated to the subject. In both trials block randomisation (block length: 10 in trial TC-021-IM, 4 in trial TC-023-IM) was applied using a randomisation ratio (TachoSil : comparator) of 1:1.

Blinding (masking)
Due to practical reasons (comparison to standard surgical and standard haemostatic treatment), blinding was not possible. Thus, the studies were performed as open-label studies.

Statistical methods
For the *efficacy analyses*, in general, statistical tests were decided applying α = 5% (2-sided). The primary analysis in both trials was performed for the ITT population comprising of all patients randomised who were treated, additional analyses were performed on pre-specified PP populations. Continuous data were summarised by the number of valid and missing values, mean, standard deviation (SD), median, minimum and maximum. Categorical data were summarised by absolute and relative frequencies.

The primary parameter of efficacy in study TC-021-IM, duration of post-operative air leakage was analysed by means of a life table analysis. Since air leakage was recorded at nominal time points, i.e. the evening on the day of surgery, 1st shift on the day after surgery etc. the actual time points of sealing were not observed but attributed to one of the time intervals Day $0_{operation}$-Day $0_{evening}$, Day $0_{evening}$ - Day $1_{morning}$, Day $1_{morning}$ - Day $1_{evening}$, etc. Subjects that did not obtain absence of air leakage were censored at the day of the last assessment. In case this assessment was missing, post-operative air leakage was censored at the time of the last available assessment. Subjects needing rescue treatment were censored at the maximum duration of post-operative air leakage (whether censored or not) among all other subjects. The Log-rank test of equality over treatments stratified for centre was performed using the life table method.
An exploratory parametric survival analysis of the primary endpoint, accounting for the interval censoring, was performed using an accelerated failure time model. The distribution of the observed event times was compared with standard distributions within the framework of accelerated failure time models. A Weibull model with factors treatment and centre was subsequently selected on the basis of log-likelihood tests. In this analysis the actual time points of air leakage assessment were used. The time to sealing was measured from the time point of the last water submersion test.
Sensitivity analyses, applying different censoring mechanisms and/or policies to substitute missing values were performed for the primary analysis model in order to assess the robustness of the study results.
The secondary efficacy parameter, reduction in intra-operative air leakage intensity after the first application of trial treatment was analysed by means of a Wilcoxon test.
All other efficacy variables were summarised by means of descriptive statistical characteristics as mentioned above.

The primary efficacy endpoint in study TC-023-IM, the proportion of subjects achieving haemostasis at 3 min in the target area was analysed using a Cochran-Mantel-Haenszel (CMH) test controlling for centre (data from small centres pooled). Homogeneity of results across (pooled) centres was assessed by means of a Breslow-Day test. The null hypothesis of no treatment was to be rejected in case the CMH test resulted in a p-value < 0.05.

The same method as for the primary endpoint was used to assess the secondary efficacy endpoint, proportion of subjects achieving haemostasis after 6 min. All other efficacy parameters were described by means of statistical characteristics.

For the *Safety analyses* in both studies, treatment emergent adverse events were coded according MedDRA version 10.1 and tabulated stratified by treatment, system organ class (SOC), preferred term (PT), severity and relation. The number of TachoSil sponges used are summarised by descriptive statistics. Laboratory values from day after surgery (only study TC-021-IM) and discharge were plotted against the values from baseline for both treatments. Changes in laboratory values from baseline were compared between treatments by means of Mann-Whitney test. Vital signs were summarised by descriptive statistics by treatment and day.

- Results

Participant flow and conduct of study
The participants' flow in both pivotal studies is summarised in the table below:

Table 3 - Participant flow in studies TC-021-IM and TC-023-IM

Trial	**TC-021-IM**		**TC-023-IM**	
Screened	486		326	
Screening failures	185		206	
Randomised	301		120	
Trial treatment	**TachoSil**	**Standard**	**TachoSil**	**Standard**
Randomised	150	151	59	61
No treatment received	2	0	0	1
ITT set	148	151	59	60
Safety set	149	150	62	57
PP set	135	138	59	52
Discontinued due to AE	2	0	2	1
Discontinued for other reason	4	2	2	5

In study TC-021-IM a total of 301 patients were randomized at 12 centres in 8 European countries. The trial took place between January 2006 (first patient in) and March 2007 (last patient out). Of note, an amendment to the protocol (Amendment 1, March 2006) discarded the testing of neo-antigenicity.
In study TC-023-IM a total of 120 patients were randomized at 10 centres in 5 European countries. The trial took place between June 2006 (first patient in) and September 2007 (last patient out).

In both trials the primary analyses were performed for the ITT population as outlined in Table 3.

Baseline data
In both trials, patients were well matched with respect to their demographic and baseline data. The main baseline data for study TC-021-IM and TC-023-IM respectively are as follows:

Table 4 - TC-021-IM, baseline data

Variable	Unit	TachoSil	Standard
Sex Male Female	 %	 69 31	 66 34
Age	years	64 (33 - 83)	64 (34 - 82)
Age > 65 years	%	49	47
Height	cm	170 (142 - 192)	169 (144 - 192)
Weight	kg	75 (42 - 128)	75 (46 – 113)
Body Mass Index	kg/m2	25.8 (15.2 - 38.6)	26.1 (17.3 - 38.6)
Ratio of smokers	%	32	31
Users of alcohol	%	30	26
Blood pressure* Systolic Diastolic	 mmHg	 134 (90 - 210) 78 (40 - 105)	 134 (100 - 210) 78 (40 – 100)
Heart rate*	/min	78 (50 - 110)	77 (40 – 128)
Respiratory rate*	/min	16 (10 - 26)	16 (8 - 23)
ECG* Abnormal (CS)	 	 24 (4)	 31 (8)
FEV-1	ml	2,477 (1,050-5,000)	2,495 (103-7,200)
TLC	ml	6,169 (2,300-9,720)	6,138 (2,520-9,780)
RV	ml	2,654 (780-7,830)	2,606 (720-7,150)

Table 5 - TC-023-IM, baseline data

Variable	Unit	TachoSil	Standard
Sex Male Female	 %	 76 24	 72 28
Age	years	65 (23 - 82)	68 (36 - 86)
Age > 65 years	%	59	65
Height	cm	170 (150 - 196)	170 (155 - 186)
Weight	kg	77 (46 - 145)	79 (45 - 118)
Body Mass Index	kg/m2	26.8 (18.3 – 50.2)	27.4 (16.5 – 37.2)
Blood pressure* Systolic Diastolic	 mmHg	 128 (100 - 170) 74 (40 - 102)	 128 (90 – 183) 73 (50 - 93)
Heart rate*	beats/min	71 (50 - 114)	73 (46 - 96)

There were no pronounced differences between treatment groups in study TC-021-IM with regard to the surgical procedures:

Table 6 - TC-021-IM, surgical variables

Variable	Unit	TachoSil	Standard
Thoracic incision			
Antero-lateral	%	56	54
Postero-lateral		44	46
Lymph adenectomy	%	97	93
Type of resection			
Right upper lobectomy	%	37	34
Right lower lobectomy		14	16
Left upper lobectomy		23	26
Left lower lobectomy		17	16
Middle lobe lobectomy		5	5
Upper bi-lobectomy		0	2
Lower bi-lobectomy		4	2
Intensity of air leakage			
Grade 1	%	52	47
Grade 2		48	52

In study TC-023-IM there was no difference in the primary haemostatic treatment between both groups:

Table 7 - TC-023-IM, primary haemostatic treatment

Primary haemostatic treatment	Unit	TachoSil	Standard
Suturing	%	73	72
None		17	20
Electro coagulation		10	8

The bleeds treated were mainly vascular and arterial, revealing no major differences between the 2 treatment groups:

Table 8 - TC-023-IM, bleedings treated

Surgical variable	Unit	TachoSil	Standard	All subjects
Target area				
Aorta	%	59	53	56
Right ventricle		19	13	16
Right atrium		9	17	13
Site of bleeding				
Vessel	%	73	63	68
Tissue		27	37	32
Type of bleeding				
Arterial	%	81	67	74
Venous		19	33	26
Severity of bleeding				
Mild (oozing)	%	32	40	36
Moderate		59	57	58
Severe		9	3	6

Study TC-021-IM primary endpoints results

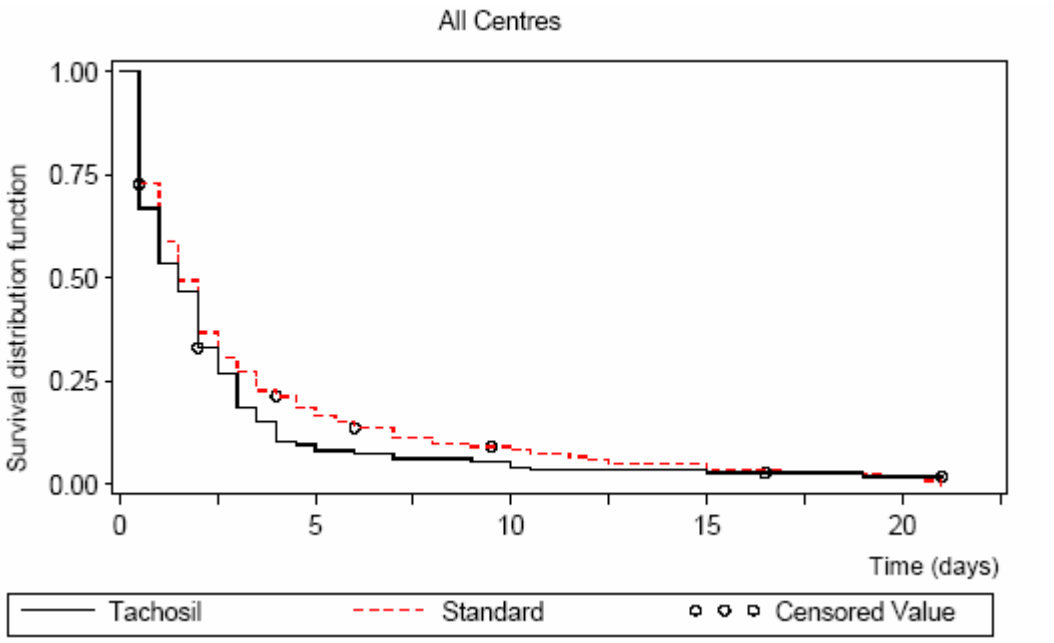
Results for the primary efficacy endpoint, duration of post-operative air leakage, are shown below for the ITT population:

Table 9 - Percentage of patients with air leakage at selected time points after surgery

Treatment	D 0 (e)	D 1 (m)	D 1 (e)	D 2 (e)	D 5 (m)	D 10 (m)	D 20 (m)
TC-S	67 %	53%	47%	27%	8%	4%	2%
Standard	73%	59%	49%	31%	17%	8%	2%

D, day; e, evening; m, morning.

Figure 1 - TC-021-IM, duration of air leakage



Thirty three percent (TachoSil) and 27% (standard treatment) of patients had no air leakage in the evening of the day of surgery. The percentage of subjects without air leakage was higher in the TachoSil group at all selected time points. This was supported by the results of a log-rank test indicating a statistically significant (p = 0.030) shorter duration of post-operative air leakage in the TachoSil group compared to standard treatment.

An exploratory parametric analysis using an accelerated failure time model, resulted in an estimated median time until cessation of air leakage of 15.3 h for TachoSil and 20.5 h for standard treatment (p=0.150).

A sensitivity analysis supports the trend in favour of TachoSil as seen in the primary analysis: when assigning the longest post-operative duration of air leakage recorded to censored observations in the TachoSil group the analysis just failed to reach statistical significance (p=0.051). To assess the impact of the use of Heimlich valves on the primary endpoint, subjects treated with Heimlich valves were consequently assigned the longest observed post-operative duration of air leakage across all subjects (20 days). This analysis resulted in a statistically significant difference in favour of TachoSil treatment (p=0.032). Also the log-rank test performed on the PP population provided statistical evidence of a shorter duration of post-operative air leakage in the TachoSil group (p=0.006).

Study TC-023-IM primary endpoints results

Haemostasis within 3 minutes was reached in 44/59 (74.6%) patients in the TachoSil group compared to 20/60 (33.3%) patients following standard treatment. This difference was statistically significant (p < 0.001, CMH-test). When analysing the PP population, similar results were observed (TachoSil: 44/59 (74.6%), standard treatment: 18/52 (34.6%), p < 0.001).

Study TC-021-IM Ancillary analyses

The secondary efficacy parameter, reduction of intra-operative air leakage intensity, revealed an advantage for TachoSil. 105/147 (71%) of patients treated with TachoSil achieved reduction of at least one grade compared to 90/145 (62%) patients in the standard group (p = 0.04).

Table 10 - Number (%) of patients with different grades of intra-operative air leakage intensity before and after randomisation

Treatment	Before randomisation				After randomisation			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
TC-S	0 (0%)	76 (51%)	72 (49%)	0 (0%)	88 (60%)	41 (28%)	18 (12%)	0 (0%)
Standard	0 (0%)	72 (48%)	78 (52%)	0 (0%)	63 (43%)	58 (40%)	24 (17%)	0 (0%)

Minor advantages for TachoSil were found in the mean number of days until chest drain removal (4.9 days TachoSil; 5.5 days standard) and days until discharge (9.3 TachoSil; 9.7 Standard)

Table 11 - Post-operative complications and additional procedures in study TC-021-IM

Variable	Unit	TachoSil	Standard
Total volume of chest tube drainage	ml	1,738 (390 - 6,590)	1,656 (190 - 5,745)
Postoperative complications*, e.g.	%	26	33
Cardiac arrhythmia		6.7	8.0
Atelectasis		6.0	7.3
Pneumonia		6.0	6.0
Additional procedures*	%	11	11
Additional chest tube drainage		4.7	4.0
Need of blood transfusion		4.7	6.0
Re-operation		4.0	3.3
Need of respiratory assistance		2.7	2.0
Inflation of the lung*			
Incomplete on e.g. Day 1	%	29	21
Pneumothorax*, e.g.			
Present on Day 1	%	38	32
Before drain removal		30	33

*: Data for the AT analysis set; Data from Tables 9,32,34

Table 12 - Details on pneumothorax, AT

Pneumothorax, details	TACHOSIL				STANDARD				All			
	N	Mean	Min	Max	N	Mean	Min	Max	N	Mean	Min	Max
DAY 1												
Apical gap (cm)	38	2.4	0.0	6.0	31	2.7	0.2	10.0	69	2.6	0.0	10.0
Gap surrounding the lung (cm)	22	0.9	0.0	6.0	10	0.7	0.0	3.0	32	0.9	0.0	6.0
DRAIN REMOVAL												
Apical gap (cm)	32	1.7	0.0	5.0	36	1.8	0.0	5.0	68	1.8	0.0	5.0
Gap surrounding the lung (cm)	14	0.6	0.0	5.0	13	1.3	0.0	9.0	27	1.0	0.0	9.0
AFTER REMOVAL												
Apical gap (cm)	38	1.7	0.0	5.0	40	1.7	0.0	5.0	78	1.7	0.0	5.0
Gap surrounding the lung (cm)	17	0.9	0.0	5.0	16	0.6	0.0	2.0	33	0.8	0.0	5.0
DISCHARGE												
Apical gap (cm)	24	1.6	0.0	5.0	28	1.9	0.1	5.7	52	1.8	0.0	5.7
Gap surrounding the lung (cm)	9	1.7	0.0	5.0	11	0.6	0.0	2.0	20	1.1	0.0	5.0
FOLLOW-UP												
Apical gap (cm)	9	2.5	0.5	5.0	7	2.3	1.0	5.0	16	2.4	0.5	5.0
Gap surrounding the lung (cm)	5	1.0	0.0	4.0	5	0.2	0.0	1.0	10	0.6	0.0	4.0

Study TC-023-IM Ancillary analyses

Haemostasis after 6 minutes was achieved in 56/59 (95%) patients treated with TachoSil and in 43/60 (72%) patients in the standard group ($p < 0.001$). In the subgroup of patients with trial treatment before protamine infusion the proportion with haemostasis at 3 minutes was in favour of TachoSil (7/10 vs. 5/9, n.s.) however for haemostasis at 6 minutes no difference was seen (9/10 vs. 8/9). For patients with trial treatment during or after protamine the proportion with haemostasis at 3 minutes was 80% (TachoSil) vs. 32% (Standard, $p < 0.001$). For haemostasis at 6 minutes there was also an advantage for TachoSil (98% vs. 75%, $p < 0.001$). Median duration of drainage was comparable between the TachoSil group (46 days) compared to standard treatment (44 days). Volume of post-operative drainage was slightly higher following TachoSil (median: 600 ml) than for standard treatment (median: 498 ml).

In a substantial proportion of patients, trial treatment was applied after surgical procedures on vessels (aorta, coronary anastomosis or pulmonary artery). An exploratory analysis (not pre-specified) was made of the efficacy of trial treatment in this subgroup, according to the defined target area of bleeding. The results are presented in Table 11, comparing the application on vessels with application on heart tissue (left/right atrium or ventricle) in ITT population.

Table 13 - TC-023-IM: Proportion of patients with haemostasis at 3 min (primary endpoint) and 6 min (secondary endpoint) after application with p-values for difference between treatments for heart and vessel application sites, respectively

Treatment	Total number of patients	Proportion of patients with haemostasis	p-value
Subgroup: target area HEART TISSUE			
Primary endpoint			
TC-S	21	0.810	0.0126
Standard	24	0.375	
Secondary endpoint			
TC-S	21	0.952	0.1591
Standard	24	0.792	
Subgroup: target area VESSEL			
Primary endpoint			
TC-S	36	0.694	0.0029
Standard	36	0.306	
Secondary endpoint			
TC-S	36	0.944	0.0043
Standard	36	0.667	

In the TachoSil group, 17 (27%) subjects had 24 intra-operative transfusions compared to 21 (37%) subjects with 25 transfusions in the control group. Post-operatively, 26 (42%) patients with TachoSil had 51 transfusions and 22 (39%) patients with standard treatment had 44 transfusions. Three (5%) TachoSil and 17 (28%) standard treatment subjects were treatment failures and received rescue treatment. The mean duration of stay in hospital was 11.4 and 13.8 days for TachoSil and control subjects, respectively. Mean duration of drainage was 93 h in TachoSil subjects and 67 h in controls with a mean volume of post-operative drainage of 1,005 ml and 932 ml, respectively. Re-operation was performed in 3 TachoSil subjects (5%) and 8 standard treatment subjects (14%). The reasons for re-operation were not related to the trial treatment and or target area. In total, 27 (44%) TachoSil subjects and 31 (54%) standard treatment subjects had other post-operative complications.

2.2.2 Discussion on clinical efficacy

Two clinical studies were submitted to support the extension of the indication to include tissue sealing and suture support in vascular surgery: study TC-021-IM in lung lobectomy surgery and study TC-023-IM in cardiovascular surgery. In both studies, the selection of the trial population and the inclusion/exclusion criteria were appropriate. Patients were well matched with respect to their demographic and baseline data and also with regard to the surgical procedures. The choice of endpoints was acceptable as well as the sample size calculation and the methods used for randomisation. Due to practical reasons (comparison to standard surgical and standard haemostatic treatment), blinding was not possible, also with respect to assessing the primary endpoint in both trials. Thus, an assessment bias cannot be completely ruled out.

In Study TC-023-IM in elective surgery on the heart, the ascending aorta or the aortic arch. TachoSil was shown to be superior to haemostatic fleece material without additional active coagulation stimulating compounds. Three minutes after application, 74.6% of patients had achieved haemostasis compared to 33.3% after standard treatment. A significant difference with respect to the secondary endpoint (proportion of patients with haemostasis after 6 minutes) has also been found. Clinical efficacy has clearly been demonstrated.

In lung surgery (study TC-021-IM) the percentage of patients without air leakage was higher in the TachoSil group at all time points compared to standard treatment, resulting in a statistically significant difference for the duration of post-operative air leakage. The estimated median time until cessation of air leakage was 15.3 h for TachoSil and 20.5 h for standard treatment. However, the results of the primary efficacy endpoint analysis of TC-021-IM study were not considered to be robust. The

statistical significance of the efficacy comparison in the ITT population is of a borderline significance. No estimated treatment difference was available thereby preventing any assessment of the clinical relevance of the difference in duration. In contrast to the ITT analysis, the PP population (performed by excluding 26 patients) revealed a much lower p-value indicating a statistically significant shorter duration of air leakage. The characteristics of 26 patients removed from the ITT analysis indicate that the air leakage duration was similar between excluded patients. In addition a critical post-hoc sensitivity analysis excluding two rescue treatment patients resulted in a significant improvement of the statistical difference of results between ITT and PP analyses in favour of TachoSil thereby indicating that the presence of the rescue treatment has penalized an air leakage duration estimates. Therefore it was viewed that an original ITT analysis of the TC-021-IM study was sufficiently conservative.

Whether the gain of an additional 5.2 hours (median) in relation to an earlier cessation of air leakage is clinically meaningful, is difficult to assess. In the median, the chest drain was removed on day 4 in the TachoSil group and on day 5 in the control group. It is acknowledged that the time of removal of the drain does not exclusively depend on the cessation of air leakage but also on the production of drain fluid and routine procedures on the hospitals' wards.

The analysis of the secondary endpoint (intra-operative air leakage) supports the results of the primary endpoint (post-operative air leakage) in favour of TachoSil. Seventy-one percent (71%) of patients achieved a reduction of intra-operative air leakage of 1-2 grades by application of TachoSil compared with 62% in the standard treatment group. Kind and number of post-operative complications or additional procedures were roughly comparable for the two treatment groups, as well as the number of blood transfusions and the days spent at hospital. However, results of the secondary endpoint analysis are considered to be of a borderline significance.

Overall, superiority of TachoSil over standard treatment has formally been shown in both studies, i.e. in lung and in cardiovascular surgery. Patients treated with TachoSil had a shorter duration of air leakage or a faster haemostasis, respectively, than patients with standard treatment.

2.3 Clinical safety

2.3.1 Study TC-021-IM and Study TC-023-IM

- Patient exposure

In the context of studies TC-021-IM and TC-023-IM, a total number of 211 patients was exposed to TachoSil, a further 207 patients to standard treatment. Patients had a follow-up of 1 month (+/- 10 days).

- Adverse events

Study TC-021-IM
A total of 270 AEs were reported during the trial period; 137 events in 66 (44%) TachoSil subjects and 133 events in 66 (44%) standard treatment subjects. Of these events, severity was mild for 198 (91 after TachoSil/107 after standard treatment), moderate for 54 (37/17) and severe for 18 (9/9) of the AEs.

Table 14 - Common AEs of the lung trial (TC-021-IM) by treatment

	Total (n=299)	**TC-S** (n=149)	**Standard** (n=150)
Pneumonia	20	10	10
Atelectasis	17	7	10
Atrial fibrillation	16	11	5
Constipation	14	5	9
Bronchopleural fistula	14	4	10
Flatulence	9	2	7
Pyrexia	9	6	3
Pneumothorax	9	4	5
Pleural effusion	7	5	2
Anaemia	7	3	4

Table 15 - All AEs (TC-021-IM) by causality and system organ class, AT, relationship to trial drug = possible

		TachoSil N=149			Standard N=150		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
TOTAL	TOTAL	6	4	6	2	1	2
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	3	2	3	-	-	-
CONDITIONS	Drug ineffective	1	1	1	-	-	-
	Pyrexia	2	1	2	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	3	2	3	2	1	2
DISORDERS	Bronchopleural fistula	-	-	-	1	1	1
	Lung disorder	1	1	1	1	1	1
	Pleural effusion	1	1	1	-	-	-
	Pneumothorax	1	1	1	-	-	-

Table 16 - All AEs (TC-021-IM) by causality and system organ class, AT, relationship to trial drug = probable

		TachoSil N=149			Standard N=150		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
TOTAL	TOTAL	6	3	6	2	1	2
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	1	1	1	-	-	-
CONDITIONS	Pyrexia	1	1	1	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	4	3	4	2	1	2
DISORDERS	Bronchopleural fistula	1	1	1	-	-	-
	Lung disorder	1	1	1	-	-	-
	Pleural effusion	2	1	2	1	1	1
	Pneumothorax	-	-	-	1	1	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	TOTAL	1	1	1	-	-	-
	Pruritus	1	1	1	-	-	-

Study TC-023-IM

A total of 328 AEs were reported; 149 events in 46 (74%) TachoSil subjects and 17 events in 44 (77%) standard treatment subjects. Of these AEs, severity was mild for 135 (70 after TachoSil/65 after standard), moderate for 151 (64/87) and severe for 42 (15/27) of the AEs. One AE was considered possibly related to trial medication: pyrexia after TachoSil, which was non-serious and of mild severity. No AEs were classified as probably related to treatment.

Table 17 - Common AEs of the cardiovascular trial (TC-023-IM) by treatment

	Total (n=119)	**TC-S** (n=62)	**Standard** (n=57)
Atrial fibrillation	32	18	14
Atrial flutter	2	2	0
Supraventricular tachycardia	2	0	2
Pleural effusion	28	14	14
Nausea	13	8	5
Hyperglycaemia	13	6	7
Haemorrhagic anaemia	11	5	6

- Serious adverse events and deaths

In *Study TC-021-IM*, 32 SAEs were reported: 19 events in 16 TachoSil and 13 events in 12 standard treatment subjects. Six events occurred in more than one subject: pneumonia (2 TachoSil/3 standard treatment subjects); pneumothorax (2/1); vocal cord paralysis of laryngeal nerve (1/2); atelectasis (2/0); post-procedural haemorrhage (1/1); bronchopleural fistula (0/2).

Table 18 - Number of SAEs in the respective treatment arm by system organ class in TC-021-IM lung trial

System organ class/ serious adverse event (preferred term)	**TC-S** (*n*= 149)		**Standard** (*n*= 150)	
	n	E	**n**	E
Cardiac disorders				
Atrial fibrillation	-	-	1	1
Gastrointestinal disorders				
Ileus	1	-	-	-
General disorders and administration site conditions				
Drug ineffective	1	1	-	-
Hepatobiliary disorders				
Jaundice	-	-	1	1
Infections and infestations				
Candida sepsis	1	1	0	0
Pneumonia	2	2	3	3
Injury, poisoning and procedural complications				
Haemothorax	-	-	1	1
Post procedural haemorrhage	1	1	1	1
Nervous system disorders				
Cerebrovascular accident	1	1	-	-
Vocal cord paralysis	1	1	2	2
Respiratory, thoracic and mediastinal disorders				
Atelectasis	2	2	-	-
Bronchial fistula	1	1	-	-
Bronchopleural fistula	-	-	2	2
Chylothorax	1	1	-	-
Lung disorder	1	1	-	-
Pleural effusion	1	1	-	-
Pneumonia aspiration	1	1	-	-
Pneumothorax	2	2	1	1
Pulmonary embolism	-	-	1	1
Pulmonary infarction	1	1	-	-
Respiratory failure	1	1	-	-

E = Number of serious adverse events reported; n = Number of patients with SAE

Of the 32 SAEs, the severity was mild for 10 (4/6), moderate for 7 (6/1) and severe for 15 events (9/6). Causality possible was given to three SAEs in three TachoSil subjects: drug ineffective (severe), pleural effusion and pneumothorax. However, in all three patients, there was an alternative aetiology for development of the event (lung cancer and lobectomy in the case of pleural effusion and in pneumothorax; incorrect application of the TC-S sponges in the case of drug ineffective).

In *Study TC-023-IM*, 58 SAEs were reported: 15 events in 8 TachoSil subjects and 43 events in 18 standard treatment subjects. Thirteen events occurred in more than one subject: atrial fibrillation (in 1 TachoSil/4 standard treatment subjects); AV block third degree (0/4); multiorgan failure (2/1); wound infection (2/0); cardiac tamponade (1/1); renal failure acute (1/1); tubulointerstitial nephritis (1/1);low cardiac output syndrome (0/2); myocardial infarction (0/2); ventricular tachycardia (0/2); sepsis (0/2); pleural effusion (0/2); pneumothorax (0/2). Of the 58 SAEs, the severity was mild for seven (2/5), moderate for 22 (7/15) and severe for 29 (6/23). No SAEs of this trial were considered possibly or probably related to treatment with TachoSil or standard treatment.

Table 19 - Number of SAEs in the respective treatment arm by system organ class in TC-023-IM cardiovascular trial

System organ class/ serious adverse event (preferred term)	TC-S (*n*= 59)		Standard (*n*=60)	
	n	E	n	E
Cardiac disorders				
Atrial fibrillation	1	1	4	4
Atrioventricular block third degree	-	-	4	4
Cardiac arrest	-	-	1	1
Cardiac tamponade	1	2	1	1
Low cardiac output syndrome	-	-	2	2
Myocardial infarction	-	-	2	2
Ventricular tachycardia	-	-	2	2
Gastrointestinal disorders				
Colitis ischaemic	-	-	1	1
General disorders and administration site conditions				
Multiorgan failure	2	2	1	1
Infections and infestations				
Mediastinitis	1	1	-	-
Pneumonia klebsiella	-	-	1	1
Postoperative wound infection	-	-	1	1
Sepsis	-	-	2	2
Staphylococcal bacteraemia	1	1	-	-
Wound infection	2	2	-	-
Wound infection staphylococcal	1	1	-	-
Injury, poisoning and procedural complications				
Brain contusion	-	-	1	1
Cardiac function disturbance postoperative	1	1	-	-
Haemothorax	-	-	1	1
Post procedural haemorrhage	1	1	-	-
Post procedural stroke	-	-	1	1
Stent-graft endoleak	-	-	1	1
Nervous system disorders				
Cerebral infarction	1	1	-	-
Cerebrovascular accident	-	-	1	1
Vocal cord paralysis	-	-	1	1
Psychiatric disorders				
Mental disorder due to a general medical condition	-	-	1	1
Renal and urinary disorders				
Renal failure acute	1	1	1	1
Tubulointestinal nephritis	1	1	1	1
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure	-	-	1	1
Pleural effusion	-	-	2	5
Pneumothorax			2	2
Pulmonary embolism			1	1
Respiratory failure			1	1
Vascular disorders				
Haemorrhage	-	-	1	1
Hypotension	-	-	1	1

E = Number of serious adverse events reported; n = Number of patients with SAE

In TC-021-IM, four subjects died: three TachoSil subjects (due to candida sepsis plus atelectasis; cerebrovascular accident (this subject died approx. 1 month after the 1-month follow-up); pneumonia aspiration plus bronchial fistula) and one standard treatment subject (due to bronchopleural fistula).
In TC-023-IM, four subjects died: two TachoSil subjects (both died due to sepsis with multi-organ failure) and two standard treatment subjects (one due to sepsis with multi-organ failure; one due to ventricular tachycardia, myocardial infarction and respiratory failure).
No death was considered related to trial treatment. All deaths were related to the underlying illness or to complications of surgery.

- Laboratory findings

The results of laboratory findings in both trials indicate no abnormalities which could be related to use of TC-S. No statistically significant differences between TachoSil and standard treatments were seen.

- Vital Signs / Physical Examination

Findings were appropriate for the severity of operations in patients for both trials.

- Safety related to drug-drug interactions and other interactions

In study TC-023-IM, most of the trial treatments were applied after reversal of heparinisation with protamine infusion. However, a subgroup of 19 subjects, 10 TachoSil and 9 standard treatment subjects, received the trial treatment before protamine infusion and interestingly 70% of the TachoSil subjects had haemostasis at 3 min. Standard treatment was less effective (56%) in this setting.

- Discontinuation due to AES

In total, five subjects were withdrawn due to AEs. In study TC-021-IM this was one patient with candida sepsis and another patient with cerebrovascular accident, both in the TachoSil group, and in study TC-023-IM, two patients in the TachoSil group and one in the standard treatment group (all due to multi-organ failure).

2.3.2 Post marketing experience

TC-S has been marketed in most EU member states since 2004. Up to June 2008 more than 830,000 sponges have been sold. Assuming an average use of two sponges per procedure approximately 415,000 patients have been exposed to TC-S in the period. No new safety concerns have been identified, and no changes of the product labelling for safety reasons have been considered necessary.

During the evaluation of this extension of indication application, the MAH submitted the results of the Post-Authorisation Safety Surveillance study TC-018-IN (Follow-up measure FUM 011). This prospective real patient safety monitoring study was initiated post marketing to allow the monitoring of thrombotic events, immunological reactions and potential interactions. The objective was to obtain systematic safety information on all patients where TachoSil is used for haemostasis in patient undergoing surgery. From the results reported there is no evidence that TachoSil causes thromboembolic events, immunological events or major bleeding, neither by itself, nor through drug interactions. (CHMP conclusions adopted on 25 September 2008).

2.3.3 Discussion on clinical safety

Clinical safety was assessed from the two clinical trials submitted with the variation application. The study population and the exposure to treatment were deemed appropriate and representative for the kind of surgery under investigation. Pyrexia occurred with a slightly higher incidence in the TachoSil treatment groups. Information regarding pyrexia remains in the SPC.

Further to the request from the CHMP in relation to cases of hypersensitivity reactions (pruritus and rash), the MAH provided an overall Clinical Expert Statement on the immunogenicity of TachoSil. Even if it cannot be totally excluded that equine collagen-related systemic hypersensitivity reactions may occur during degradation of the sponge, the CHMP agreed that these events could be regarded as single cases and that adequate information is already provided in sections 4.3 (contraindications) and sections 4.4 (Special warnings and precautions for use) of the SPC.

Slightly higher incidence of atrial fibrillation (mainly reported by the MAH as non-serious AE) in TachoSil treated patients in the trials in lung lobectomy and cardiovascular patients raised a concern during the evaluation of this application. However, the additional data provided by the MAH on patients with episodes of atrial fibrillation indicate that there is insufficient evidence at present to suggest a plausible link between TachoSil and atrial fibrillation. Narratives of patients indicate that atrial fibrillation events were of transient nature and occurred in patients who had baseline risk of cardiovascular morbidity. The size of the clinical database of the MAH (inclusive TC-018-IN study) with more than 3600 patients treated with TachoSil is more adequate now to address the concern on thrombotic and cardiac risks and provided data are reassuring.

Overall, results from these two studies did not reveal any new safety concerns. Adverse events were in general comparable between the treatment arms and related to the underlying or concomitant diseases and/or the surgical procedures.

3. Risk Management plan (RMP)

The MAH submitted a risk management plan.

The final agreed RMP version 3.0 includes as identified risk thromboembolic events and as potential risks immunological events, transmission of infectious agents, drug-drug interactions, atrial fibrillation, pyrexia and off-label use for sealing indication.

The following Important missing information has been identified in the RMP version 3.0:

- Specific data has not been obtained on the use of TachoSil in neurosurgery or in gastrointestinal anastomosis.
- The safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials.
- Repeated use of TachoSil.

Table 20 - Summary of the Risk Management Plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Thrombo-embolic events	Routine pharmacovigilance	Current approved SmPC: 4.2 Posology and method of administration The use of TachoSil is restricted to experienced surgeons. 4.4 Special warnings and precautions for use For local use only. Do not use intravascularly. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly. 4.8 Undesirable effects Vascular disorders: Thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.
Immune-mediated reactions	Routine pharmacovigilance	Current approved SmPC: 4.3 Contraindications Hypersensitivity to the active substances or to any of the excipients. 4.4 Special warnings and precautions for use As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately.

		In case of shock, the current medical standards for shock treatment should be observed. 4.8 Undesirable effects Immune system disorders: Hypersensitivity or allergic reactions may occur in rare cases in patients treated with fibrin sealant. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. Investigations: Antibodies against components of fibrin sealant products may occur rarely.
Transmis-sion of infectious agents	Routine pharmacovigilance	Current approved SmPC: 4.4 Special warnings and precautions for use Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia). It is strongly recommended that every time that TachoSil is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Drug interactions	Routine pharmacovigilance	Current approved SmPC: 4.5 Interactions with other medicinal products and other forms of interactions No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the sealant may be denaturated after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the sealant.
Atrial fibrillation	1) Routine pharmacovigilance 2) Expedited reporting of all cardiac events from post-marketing exposure 3) Outlining of cardiac events in a separate section in the PSUR	Please refer to section regarding thromboembolic events.
Pyrexia	Routine pharmacovigilance	Current approved SmPC: 4.8 Undesirable effects General disorders and administration site condition: Pyrexia may occur commonly.
Off-label use (sealing)	Routine pharmacovigilance	Current approved SmPC: 4.1 Therapeutic indications TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. 4.4 Special warnings and precautions for use Specific data has not been obtained on the use of this product in neurosurgery, in vascular surgery or in gastrointestinal anastomosis.

The CHMP, having considered the data submitted in the application and the results of the Post marketing safety monitoring study (TC-018-IN) is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Benefit-risk assessment

TachoSil is a ready-to-use absorbable medicated sponge, developed for support of haemostasis and tissue sealing. It consists of an equine collagen sponge coated with human Fibrinogen and human Thrombin, which are well-established components of fibrin sealants. Tissue sealing/adhesive and haemostatic properties of this product are non-separable and can not be exerted without one or another. The overall haemostatic efficacy of TachoSil has been demonstrated by the MAH in the previous clinical trials in abdominal surgery (liver and kidney resections). However according to the Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products (CPMP/BPWG/1089/00), a new clinical study needs to be conducted to support any new indication of the fibrin sealant/haemostatic products.

The efficacy evidence supporting this variation application was obtained by the MAH from two clinical trials: promotion of tissue sealing was investigated in both trials by applying TachoSil on lung

tissue and on heart muscle tissue with endpoints of air and blood leakage, respectively. Additionally, the efficacy of TachoSil as suture support in vascular surgery was investigated, since 68% of the patients in the cardiovascular study had surgery of vessels. Both studies formally demonstrated superiority of TachoSil over standard treatment.

The efficacy evidence derived by the MAH from cardiovascular surgery trial comparing the haemostatic efficacy of TachoSil versus the standard treatment was robust and adequate enough to endorse the extension of the indication for suture support in vascular surgery.

Although the evidence derived from lung lobectomy surgery trial is less robust, the analysis of the primary efficacy endpoint in this TC-021-IM study is of borderline but statistically significant value. The characteristics of 26 patients removed from the ITT analysis indicate that the air leakage duration was similar between excluded patients. In addition a critical new post-hoc sensitivity analysis excluding two rescue treatment patients resulted in a significant improvement of the statistical difference of results between ITT and PP analyses in favour of TachoSil thereby indicating that the presence of the rescue treatment has penalized an air leakage duration estimates. Therefore, it was viewed that an original ITT analysis of the TC-021-IM study was sufficiently conservative.

The indication of tissue sealing will cover various types of surgery and it is considered that the surgical settings selected by the applicant in the lung surgery were reasonably conservative. The lung surgery study TC-021-IM included patients with lung cancer who potentially had underlying chronic obstructive pulmonary disease, emphysema and pulmonary fibrosis. Therefore the adhesiveness and withstanding against the air pressure/air leak properties may challenge the effectiveness of TachoSil. Considering that the results of TC-021-IM study are less convincing but still statistically significant, it is possible to expect that in lesser challenging surgical settings TachoSil will produce more robust efficacy in tissue sealing settings. Based on statements provided by two thoracic surgeon experts, TachoSil could be of better use especially in patients with advanced emphysema and fibrosis since the presence of fragile lung tissue makes stapling and clamping techniques limited or impossible.

An optimal ratio between the standard treatment and the TachoSil application will depend on the individual patient's needs and the status of lung tissue remodelling. The surgeon can make decision on how adjunctive/supportive TachoSil can be in addition to conventional reinforcing tissue sealing techniques such as stapling and clamping. The difference in few hours in relation to chest-drain removal between groups although not very convincing, still translates in gain of 1 chest-drain free day.

Clinical advantages of using TachoSil were adequately supported with a number of previous clinical studies. The product has shown a robust and good efficacy in haemostatic support in different surgical settings. A tissue sealing component of TachoSil effect in extra-pulmonary applications was evident from studies conducted in abdominal and cardiovascular surgeries.

Overall, the safety profile of TC-S appears to be good. No major safety concerns derived from these two new studies. Causes of deaths in both trials supporting this application seem to be unrelated to use of the product. Section 4.8 of the SPC was updated further to the additional data provided in this application and reformatted as a table according to MedDRA terminolofy and frequency grouping.

In conclusion, the benefit-risk profile of the product is considered to be positive to promote tissue sealing, and for suture support in vascular surgery and therefore, the CHMP agreed for the indication to be extended as follows:

"TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis, *to promote tissue sealing, and for suture support in vascular surgery* where standard techniques are insufficient (see SPC section 5.1)".