

**Office of Biostatistics and Epidemiology/Division of Epidemiology
TachoSil® Pharmacovigilance Final Review Memo**

Subject: BLA STN: 125351
Product: TachoSil
Sponsor: Nycomed Danmark ApS
Indication: Adjunct to hemostasis in cardiovascular surgery

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I. Introduction

OBE/DE/TBSB has completed a review of the BLA STN 125351, an original BLA for TachoSil, a fibrin sealant patch used as an adjunct for hemostasis in cardiovascular surgery. The purpose of this review is to identify potential safety issues, review proposed pharmacovigilance activities, and assess their adequacy for safety monitoring should this product be licensed. Information on the clinical studies and safety data in this review is derived from the clinical summaries presented in the TachoSil BLA, including the Clinical Overview (Section 2.5), the Summary of Clinical Safety (Section 2.7.4 (includes safety data form the all studies data pool), the study reports of post approval studies TC-018-IN and TC-019-IN (Section 5.3.5.2), the 120-day Safety Update to the Summary of Safety, Submitted 9/7/2009, and the Pharmacovigilance Plan (PVP) (Section 5.3.6).

Large sections of text and tables taken from the sponsor are denoted in italics. Other sections quoted or paraphrased from the sponsor are referenced to the appropriate section of the BLA.

II. Product Background

TachoSil fibrin sealant patch is a collagen sponge of equine origin. The active side of the sponge, which is coated with human fibrinogen and human thrombin, is marked as yellow in color. The mechanism of action of TachoSil follows the principles of fibrin clot formation. When in contact with bleeding or a leaking wound surface, the coating of the collagen sponge dissolves and the thrombin-fibrinogen reaction initiates the coagulation cascade (BLA 2.5.1.2). The sponge is designed to be applied topically to the tissue surface to support intraoperative hemostasis and -----(b)(4)----- and be left in situ (BLA 2.2). All components of the product, including the collagen sponge, are expected degrade in about -(b)(4)- months (BLA 2.5.1.2).

Indication and Dosage

Tachosil is indicated as an adjunct to hemostasis in cardiovascular surgery. It has been proven effective, per sponsor, -----(b)(4)-----.

The number of sponges to be used depends on the size of the wound area to be treated. TachoSil is administered as a single dose treatment during surgery. The patch is available in 3 sizes: 9.5cm x 4.8cm, 4.8cm x 4.8cm, and 3.0cm x 2.5cm. TachoSil contains 5.5 mg fibrinogen and 2.0 IU thrombin per square cm(BLA 3.2)

Market Experience

TachoSil was first approved in Europe in 2004 for improvement of hemostasis in surgery where standard techniques are insufficient. In 2009, the European Commission also approved TachoSil to promote tissue sealing and for suture support in vascular surgery where standard techniques are insufficient (BLA 2.2). TachoSil has been marketed in 30 countries outside the U.S. since 2004. The only difference between the European and US TachoSil products is that the active substances Human Fibrinogen and Human Thrombin contained in TachoSil for the U.S. market are manufactured from human plasma derived from FDA licensed centers only. This BLA represents the first regulatory submission for marketing approval in the U.S. (BLA 2.2)

III. Clinical Trials Summary

Safety specification is based on 6 randomized, controlled clinical trials of TachoSil:

- (b)(4)--IN -----(b)(4)-----
- (b)(4)--IN -----(b)(4)-----
- (b)(4)--IN -----(b)(4)-----
- (b)(4)--IN -----(b)(4)-----
- (b)(4)--IM -----(b)(4)-----

TC-023-IM Cardiovascular

There were a total of 1,038 adult patients in these 6 studies randomized to either TachoSil or comparator, and these data are integrated into the **all studies data pool**.

3 additional ongoing studies include -----(b)(4)----- . **These ongoing studies were not reviewed as part of this safety review.**

IND-(b)(4)- is an additional study (protocol -----(b)(4)-----) that will be conducted in the US and will assess TachoSil use -----(b)(4)-----

-----.” The trial population will consist of 224 randomized adult patients (17 years of age or older). This study includes pediatric patients: newborn and infants aged 0-23 months (inclusive), children aged 2-11 years (inclusive), and adolescents aged 12-16 years (inclusive). Inclusion in each separate age group will be stopped when 10 patients have been randomized. Inclusion of any pediatric patients will be stopped when reaching a maximum of 20 pediatric patients or when inclusion of adult patients is stopped. The primary efficacy variable is the proportion of patients with intraoperative hemostasis at target bleeding site within 3 min of application of randomized treatment.

Demographics in Clinical Trials

Nearly all patients (99.8%) in the Tachosil clinical development program were Caucasian (BLA 2.5.1.4.4). One ongoing study (---(b)(4)---) is conducted in Japanese patients. The sponsor notes that a difference in overall hemostasis function among different ethnicities has not been demonstrated in literature (BLA 2.5.1.4.4). *The mean age of all patients was 62.1 years and there were more males than females in the studies (64.6% versus 35.4%) (120-day Update, Section 2.7.4.1.3).*

Observational Studies

The sponsor has initiated 2 additional studies as post approval commitments in Europe:
 TC-018-IN observational cohort study
 TC-019-IN pediatric liver surgery trial
 Study TC-018 IN and TC-019-IN are uncontrolled studies intended to evaluate safety of TachoSil in general usage according to the European marketing authorization (TC-018-IN) and in pediatric patients (TC-019-IN) (BLA Section 2.5.1.4.2).

The sponsor’s submission provided the following summary table of studies.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Phase III Two arms Efficacy and safety	(b)(4)	5.3.5.1	To compare (b)(4) efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intraoperative (b)(4)	Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Standard surgical treatment (sutures)	TachoSil Topical, intraoperative Application	189	Patients having (b)(4) (b)(4)	Single application	Reported Full report
Phase III Two arms Efficacy and safety	(b)(4)	5.3.5.1	To compare (b)(4) efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intraoperative (b)(4)	Open, randomized, prospective, multicenter, 2-arm, parallel-group study. Control: Standard surgical treatment (sutures, staples, or no treatment)	TachoSil Topical, intraoperative Application	301	Patients having (b)(4) (b)(4)	Single application	Reported Full report

Phase IV Two arms Efficacy and safety	TC-023-IM	5.3.5.1	To compare the efficacy and safety of TachoSil versus standard hemostatic treatment in cardiovascular surgery	Open, randomized, prospective, multicenter, 2-arm, parallel-group study	TachoSil Topical, intraoperative Application	119	Patients having elective surgery on the heart, the ascending aorta or arch, requiring a cardiopulmonary by-pass procedure, and having bleeding from the heart muscle, pericardium, a major vessel or vascular bed that required supportive hemostatic treatment	Single application	Reported Full report
Phase III Two arms Efficacy and safety	(b)(4)	5.3.5.1	Comparison of efficacy and safety of TachoSil versus (b)(4) (b)(4)	Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: (b)(4)	TachoSil Topical, intraoperative Application	121	Patients requiring elective (b)(4) for any reason, with minor or moderate hemorrhage persisting after primary surgical hemostatic procedures of the major vessels	Single application	Reported Full report
Phase III Two arms Efficacy and safety	(b)(4)	5.3.5.1	Comparison of efficacy and safety of TachoSil versus standard treatment	Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Standard surgical treatment (b)(4)	TachoSil Topical, intraoperative Application	185	Patients ≥18 years requiring (b)(4) (b)(4)	Single application	Reported Full report
Phase IV	(b)(4)	5.3.5.2	To collect data on patients intra-operatively treated with hemostatic supporting agents/techniques in addition to the standard surgical procedures.	Noninterventional, nonrandomized study Control: Other agents (b)(4) (non sealants, poly-saccharides, collagen fleece, others)	TachoSil Topical, intraoperative Application	616	Patients undergoing (b)(4) (b)(4) where a hemostatic agent is used.	Single application	Reported Full report
Phase IV	(b)(4)	5.3.5.2	To gather knowledge about the routine application of TachoSil as an approved pharmaceutical product for hemostasis in (b)(4)	Prospective, noninterventional, open-label cohort study	TachoSil Topical, intraoperative Application	169	Patients undergoing elective or acute (b)(4)	Single application	Reported Full report
Comparative trial Efficacy and Safety	(b)(4)		To compare the efficacy and safety of TachoSil and TachoComb	Multicenter, double-blind, randomized, comparative, noninferiority study Control: TachoComb	TachoSil and TachoComb Topical, intraoperative Application	100 planned	Patients undergoing elective (b)(4)	Single application	Ongoing No report available yet
Phase II, single arm Method trial	(b)(4)		To evaluate if the application of TachoSil on a (b)(4) (b)(4) is feasible and safe.	Multicenter, open-label, non-randomized study	TachoSil Topical, intraoperative Application	30 planned	Patients undergoing elective (b)(4) (b)(4)	Single application	Ongoing No report available yet

Phase IV	(b)(4)		To gain knowledge about the routine application of TachoSil for hemostasis in (b)(4) surgical procedures.	Multicenter, open, prospective, noninterventional study Control: Standard treatment	TachoSil Topical, Intraoperative Application	500 planned	Patients undergoing (b)(4) (b)(4)	Single application	Ongoing No report available yet
Report of analysis of data from more than one study	ISE	5.3.5.3	Integrated Summary of Efficacy						
Report of analysis of data from more than one study	ISS	5.3.5.3	Integrated Summary of Safety						
Related information	Clinical Expert Statement	5.3.5.4	Evaluation of immune-mediated reactions against TachoSil						

IV. Safety Database

Of the 1,032 patients included in the **All Studies data pool**, 521 subjects were treated with TachoSil (BLA 120 day Safety Update, Section 2.7.4.1.2). 247 (47.4%) in the TachoSil group and 238 (46.6%) from the comparator group experienced an adverse event. The majority of the AE's were mild to moderate (BLA 2.7.4, p. 8). *The only individual AEs reported in more than 5% of patients in either treatment group were atrial fibrillation (32 patients [6.1%] in the TachoSil group and 30 patients [5.9%] in the comparator group) and pyrexia (30 patients [5.8%] in the TachoSil group and 25 patients [4.9%] in the comparator group (BLA 2.7.4.2.1.4). There was a slightly higher incidence of pyrexia, nausea, respiratory failure, wound infection, pruritus, and procedural site reactions in the TachoSil group and a slightly higher incidence of pneumonia, pneumothorax, atelectasis, bronchopleural fistula, flatulence, urinary tract infection, and decreased hemoglobin in the comparator group. However, overall the pattern of AEs observed was similar in the 2 treatment groups (BLA 2.7.4, p. 8).*

Of the 1032 patients included in the All Studies Data Pool, 10 TachoSil patients (1.92%; 95% confidence interval 0.92-3.5%) and 11 (2.15%) of the comparator treatment patients (95% CI 1.08% to 3.82%) experienced at least one thromboembolic event at some time during the trials. *The Odds Ratio of TachoSil vs. comparator for TEEs was .89 and the Relative Risk was .89, indicating no difference between TachoSil and comparator (PVP 5.3.6).*

During post-licensure adverse event surveillance surveillance in Europe, the number of spontaneous adverse events reported is 19 reports in 16 patients. There were 2 thromboembolic events occurring in 2 patients.

Hemostasis Studies Pool

------(b)(4)-----
-----, the final review of the application considered safety data from only the studies in which TachoSil was evaluated as an adjunct to hemostasis. Pooled data from the hemostasis studies (------(b)(4)----- TC-023-IM) included 544 patients randomly assigned and treated with TachoSil (n=276) or comparator treatment (n=268). In these pooled hemostasis studies, Adverse events (AEs) were reported in 142 patients (51.4%) in the TachoSil group and 130 patients (48.5%) of the

comparator group (BLA 2.7.4.2.1.4). the most commonly reported AEs were pyrexia, atrial fibrillation, pleural effusion, and nausea. Each of these AEs was reported at a slightly higher incidence for TachoSil than for the comparator treatment but the numbers of patients were small and not statistically significant.

Study TC-018-IN (observational cohort study)

These data are not included in the “all studies data pool”.

There were 3,098 patients involved. Data were collected from 227 surgical departments in 12 countries.

The following three adverse events were reported in the study

- Thromboembolic Events
- Immunologic Events
- Major Bleeding Events

There were 124 Adverse Events reported. Of these, there were 51 thromboembolic events in 46 patients, 9 immunologic events in 8 patients, and 64 major bleeding events in 62 patients. There were 156 deaths reported (BLA Section 2.7.4, p. 11). 7 deaths were attributed to thromboembolic events and 8 deaths were attributed to major bleeding events. Narrative reports on all cases were reviewed, and it is the opinion of this reviewer that all cases were related to expected post operative complications.

Thromboembolic Events

Because of TachoSil’s active ingredients and mechanism of action (*human fibrinogen and human thrombin*), the sponsor reviewed thromboembolic events in clinical studies (BLA 2.7.4.2.1.7.2, p. 74). In the all studies data pool, *the incidence of all thromboembolic events was low and was similar in the TachoSil and comparator treatment groups (1.9% and 2.0%, respectively). None of these AEs were considered to be related to study treatment by the investigator (BLA 2.7.4.2.1.7.2, p. 74).*

Estimates of the incidences of thromboembolic events, immunological events, and major bleeding based on data from 3,098 patients were available from the noninterventional study TC-018-IN. In this study, 46 patients (1.5%) had at least one thromboembolic event at any time during the study. 41 patients had a serious thromboembolic event, of which 3 patients had an event possibly or probably related to TachoSil (BLA 5.3.5.2.3, p. 32).

There were 156 deaths reported; 7 from a thromboembolic event and 8 from a major bleeding event. *None of the 7 thromboembolic events or 8 bleeding events leading to death were considered to be related to TachoSil (BLA 5.3.5.2.3, p. 32).*

The thromboembolic events in study TC-018-IN included cases of: a 51 yo male in Greece with lung cancer and ARDS who developed pulmonary embolus on post op day 19; a 78 yo female in Sweden with atherosclerosis, diabetes mellitus, and hypertension who developed coronary artery thrombosis 4 months post op; a 67 yo female with carcinoma of the larynx, diabetes mellitus, and hypertension who developed a pulmonary embolus 8 days post op; a 75 yo male in Spain who developed pulmonary embolus 5 months after surgery for colon cancer; a 74 yo male in France who developed pulmonary embolus at an unspecified date after treatment for bladder cancer; a 66 yo male in France with atherosclerosis who developed arterial mesenteric thrombosis after

treatment for colon cancer; and a 73 yo male in Germany who developed presumed pulmonary embolus after splenectomy for post traumatic bleeding (BLA 5.3.5.2.22).

Major Bleeding Events

In the all studies pool, *the incidence of bleeding events was also similar in the TachoSil and comparator treatment groups (7.1% and 9.2%, respectively), and there was no apparent evidence for an increase in bleeding events with TachoSil (BLA Section 2.7.4, p. 10).*

In the study TC-018-IN, 62 patients (2.0%) experienced at least one major bleeding event (including 55 events that were serious and 8 deaths). Seven patients had a serious major bleeding event related to TachoSil. The deaths were from post operative bleeding, multi-organ failure and DIC. All patients are surgical patients, subject to the usual post operative complications (BLA 5.3.5.2.22). The major bleeding events included: a 70 yo male in France who developed a gastrointestinal (GI) bleed 8 days post surgery for pancreatic carcinoma, felt to be due to duodenal ulceration; a 37 yo male with aspergillosis and bronchoarterial fistula who developed hemoptysis post op day 24 after lung transplantation; a 57 yo female in Germany who developed bleeding from a pancreatic fistula 30 days after surgery for duodenal carcinoma; a 53 yo female in Denmark who developed hemorrhage after treatment for esophageal carcinoma; a 70 yo male in Spain who developed hemothorax 7 days after surgery for treatment of liver cancer and cirrhosis; an 84 yo male in Greece who developed a GI bleed and DIC 36 days after treatment for esophageal cancer; a 73 yo in France who experienced sigmoid thrombosis from thromboembolism after cholecystectomy; and a 47 yo male in France who experienced bleeding post op day 42 (5.3.5.2.22).

Immunogenicity

Because TachoSil involves fibrinogen and thrombin of human origin and collagen of equine origin, the sponsor also examined the potential for immunologic reactions during clinical studies. In the all studies pool, *no patients treated with TachoSil reported AEs coded in the SOC of Immune System Disorders compared with 6 patients (1.2%) in the comparator group. Since immunological reactions could also be reported in other SOCs, a clinical expert in immunology reviewed all AEs reported in the clinical studies (see ISS, Section 18.1). This expert review concluded that no immune-mediated AEs were reported in any of the 6 studies included in the integrated analyses. No immune-mediated AEs were reported, as assessed by an external clinical expert (BLA Section 2.7.4.2.1.7.3, p. 74).*

In the noninterventional study TC-018-IN, *8 patients (0.3%) experienced at least 1 immunological event at any time during the study (5 events were mild, 3 moderate, and none severe). The most common immunological events included rash or pruritic rash experienced by 3 patients. No immunological events were reported during surgery. Between surgery and discharge, 3 patients had immunological events. Only one of the 8 events was serious but was not considered to be related to TachoSil (BLA 5.3.5.2.3, p.34).*

No specific immunologic monitoring was conducted during the clinical trials, and there is minimal clinical experience on re-exposure to TachoSil. Two patients received TachoSil twice during study TC-018-IN, and neither is reported to have developed an immune-mediated event. The interval between exposures is not reported.

From the spontaneous adverse event reporting in Europe, which the sponsor estimates involves approximately 415,000 patient exposures, as of June 2008, there were 6 adverse event reports from 4 patients of potential immune-mediated reactions to TachoSil (BLA 5.3.5.2.3 and Clinical Expert Statement 5.3.5.4)

Important potential risk- Transmission of infectious agents

No viral infections were reported as AEs from clinical trials. Two cases of hepatitis C have been reported by spontaneous reporting since approval. These adverse events were judged by the reporting clinicians as unlikely to be causally related to TachoSil.

Study TC-019-IN (Pediatric Liver Surgery)

Sixteen children ages 1.5-147.5 months undergoing liver resection with/without segmental liver transplantation were treated with TachoSil. Fourteen patients completed the 6 month follow up: one died of overwhelming sepsis leading to multi organ failure, and one required re-transplantation due to chronic graft rejection. *A total of 108 AEs were reported. Fourteen of the 16 patients reported 64 AEs on standard AE forms but none were considered related to treatment with TachoSil. In addition, there were 29 episodes of postoperative infections in 12 children and 5 children needed a total of 9 reoperations. Four children on 6 occasions showed symptoms of graft rejection (BLA 2.7.4, p. 11).*

Postmarketing Safety Data

Up to 31 December 2008, it is estimated that approximately -(b)(4)-- patients have been exposed to TachoSil, calculated based on the world-wide sales and assuming an average of 2 patches for each surgical procedure. In this period, 37 adverse drug reactions have been spontaneously reported for 30 patients. Thirty-one reactions were considered to be serious and 6 were nonserious. No new safety concerns are raised by these data. Since approval of TachoSil in Europe (8 June, 2004), 2 cases of HCV have been reported as adverse reactions. However, it was concluded that there was no temporal or lot-related cluster of case reports, and a causal relationship between TachoSil and the 2 cases of HCV was considered not likely (BLA Section 2.7.4.2).

V. Pharmacovigilance Planning

Summary of Sponsor's Pharmacovigilance Plan

Summary of important identified risks, potential risks and missing information:

The safety specification is based on all studies from the integrated summary of safety (six controlled clinical trials of TachoSil), two studies initiated as post approval commitments for Europe and post-marketing spontaneous reporting data from 8 June 2004-8 June 2008 with an estimated patient exposure of 415,000 patients. Safety data generally reflects the type of post-operative complications seen in the setting in which TachoSil is used. There does not seem to be a specific pattern for adverse events.

Important potential risk- Drug-drug interactions

No drug interactions were reported.

Important missing information- There is no data on use in neurosurgery, gastrointestinal anastomosis, pregnancy and breastfeeding, or repeat exposure.

Routine Pharmacovigilance Plans

Routine pharmacovigilance includes:

- *Systems and processes to ensure that information about all suspected adverse reactions that are reported to Nycomed are collected and collated in an accessible manner.*
- *The preparation of reports for regulatory authorities, including expedited adverse drug reaction reports and periodic safety update reports.*
- *Continuous monitoring of the safety profile of approved products, including signal detection, issue evaluation, updating of labeling and liaison with regulatory authorities (PVP, Section 1.2).*

Summary of planned pharmacovigilance actions

Based on the data from the Safety Specification, the sponsor concludes that further pharmacovigilance (beyond routine pharmacovigilance practices, the completed post-marketing study (TC-018-IN), and a planned -----(b)(4)----- study ----(b)(4)-----, is not necessary (PVP, 1.3). Study ----(b)(4)----- will include immunogenicity testing of blood samples before and after surgery with TachoSil, -----(b)(4)----- following TachoSil exposure.

An ongoing phase 3 study on use in liver surgery, IND-(b)(4)-, will proceed until January 2010, and will provide additional safety information. Additional ongoing IND studies include TC-029-IM for use in -----(b)(4)-----, and -----(b)(4)-----.

VII. Assessment and Recommendations

1. Safety Concerns

The components of TachoSil have a long history of being relatively safe. This product has been approved in the EU since 2004 and has been in wide use. However, fibrinogen and thrombin are thrombogenic substances that could potentially provoke thromboembolic adverse events. In addition, the presence of equine derived collagen (foreign protein) as a substrate introduces the theoretic possibility of immunogenicity. Thus, the primary safety concerns for post-market planning include thrombogenicity and immunogenicity. The rates of thromboembolic events (TEEs) were generally low during the clinical trials (<2%) and were the same in the treatment and comparator groups. TEEs are a known complication of surgical procedures, so TEEs in TachoSil patients, who receive the product as part of a surgical procedure, are expected and not necessarily an effect of the product. Further, the large observational study (TC-018-IN) of over 3,000 patients specifically assessed TEEs and found a rate of TEEs (1.5%) in real-world use that was consistent with the rate in the clinical trials. As discussed in Section IV above, some patients experiencing TEE in this study had pre-disposing risk factors for thromboses in addition to their surgery, including cancer and atherosclerosis.

Because TachoSil involves fibrinogen and thrombin of human origin and collagen of equine origin, immunologic reactions are also important potential AEs. In the all studies pool, immunologic reactions were observed in comparator patients but not in the treatment group, and in study TC-018-IN few (8, 0.3%) immunologic events were observed, of which, only one was serious. Immunogenicity does not seem to be a significant issue with TachoSil based on these findings, however, monitoring and assessment of immunologic AEs during routine post-licensure surveillance should continue.

2. Proposed PV Plan

Clinical trials are often limited in terms of patient population size and homogeneous nature of participants. However, there is extensive post-marketing experience already available in Europe for TachoSil, as well as the large observational study now completed (TC-018-IN). Overall, the types of adverse events reported were, in the opinion of this reviewer, consistent with the types of adverse surgical events expected in this patient population. It is unlikely that there are additional safety concerns or a difference in severity or prevalence of known adverse events that has not been detected in the clinical trials or during the post-marketing experience of TachoSil. The routine pharmacovigilance activities, as outlined by the sponsor, are acceptable.

Nycomed is pursuing additional efficacy and immunogenicity data after licensure ----(b)(4)----
----- (US IND -(b)(4)-) and additional safety data from this study will add to the available safety database.

Letter-Ready Comments

1. Other fibrin sealant products containing fibrinogen and/or thrombin have occasionally been related to thrombogenicity and/or immune mediated coagulopathy.
2. In addition to routine pharmacovigilance procedures, the ongoing study under US IND -(b)(4)- should suffice for post marketing safety surveillance.