Summary Basis for Regulatory Action

Date	31 March 2010
From	Natalya Ananyeva, Ph.D., Committee Chair
Subject	Summary Basis for Regulatory Action
BLA #	STN 125351/0
Applicant	Nycomed Danmark ApS
Date of Submission	June 5, 2009
PDUFA Goal Date	April 5, 2010
Proprietary Name / Established names	TachoSil / Fibrin Sealant Patch
Dosage forms	Apply on the surface of tissue only. Do not use intravascularly. The number of TachoSil patches to be applied should be determined by the size of the affected area. TachoSil is supplied in the following pack sizes: • Package with 1 patch of 9.5 cm x 4.8 cm • Package with 2 patches of 4.8 cm x 4.8 cm • Package with 1 patch of 3.0 cm x 2.5 cm • Package with 5 patches of 3.0 cm x 2.5 cm Strength: TachoSil contains per cm^2: Human fibrinogen 3.6-7.4 mg (mean = 5.5 mg); Human thrombin 1.3-2.7 Units (mean = 2.0 Units).
Proposed Indication	TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery when control of bleeding by standard surgical techniques, such as suture, ligature or cautery, is ineffective or impractical.
Orphan Designation	No
Recommended Action:	Approval
Signatory Authorities Action	**Jay S. Epstein. M.D._____** *Offices Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* **Mary Malarkey_____** *Offices Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a*

	separate review or addendum

Material Reviewed	Reviewers and consultants
Clinical	Nisha Jain & Kimberly Lindsey
Bio-Statistics	Jessica Kim & Chunrong Cheng
Pharmacology/Toxicology	La'Nissa Brown
CMC - Product/Facilities	Natalya Ananyeva, Laura Wood, Tim Lee & Martha O'Lone
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Bioresearch Monitoring	Lillian Ortega & Anthony Hawkins
Advisory Committee	Not presented
Labeling	Jean Makie
Clinical Pharmacology	Iftekhar Mahmood
Epidemiology	Faith Barash

1. Introduction

Nycomed Danmark ApS (Nycomed) submitted an original Biologics License Application (BLA) for a ready-to-use, degradable Fibrin Sealant product developed for application on tissue surfaces only, with the proprietary name TachoSil. TachoSil is a Fibrin Sealant Patch where two active substances – Human Fibrinogen and Human Thrombin – are coated onto an Equine Collagen Sponge to facilitate their application to the wound area in clinical practice. TachoSil is a combination product where the Equine Collagen Sponge is classified as a Medical Device. The Collagen Sponge serves as a flexible and mechanically stable carrier for the active substances to ensure their position. Riboflavin is present as a yellow colorant to indicate the active side of the patch. Human Fibrinogen Active Substance and Human Thrombin Active Substance are supplied by ----------(b)(4)----------.

TachoSil is Nycomed's third-generation Fibrin Sealant Patch product. Its predecessors are TachoComb (a collagen patch combined with used bovine thrombin and bovine aprotinin as the antifibrinolytic agent) and TachoComb H (a collagen patch containing human thrombin and bovine aprotinin). TachoComb was first marketed in Austria and Germany in 1991/1992. TachoComb H was marketed in Germany and Austria from 2001 – 2005. Compared to the predecessor products, TachoSil is free of bovine components as both Active Substances are of human origin. In addition, TachoSil does not contain bovine aprotinin. Aprotinin was removed from the formulation because it was shown not to affect fibrinolysis when contained in TachoComb and TachoComb H.

TachoSil was approved in Europe in June 2004. In February 2009, the European Commission approved the extended scope of TachoSil indications "for supportive treatment in surgery for improvement of hemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient". More than 400,000 patients have been treated in the European Union with TachoSil since June 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 US market are manufactured from human plasma derived from FDA-licensed centers only. TachoSil is

produced in three sizes: Standard (9.5 cm x 4.8 cm = 45.6 cm²), Midi (4.8 cm x 4.8 cm = 23.0 cm²) and Mini (3.0 cm x 2.5 cm = 7.5 cm²).

Nycomed claims the clinical indication for Fibrin Sealant Patch ***as an adjunct to hemostasis in cardiovascular surgery when control of bleeding by standard surgical techniques, such as suture, ligature or cautery, is ineffective or impractical.***

2. Background

Nycomed submitted the original BLA for TachoSil on 5 June 2009 with the following two proposed indications as:

----------(b)(4)----------
(2) An adjunct to hemostasis in cardiovascular surgery

At the mid-cycle of the review process, a number of issues were identified by the clinical and statistical reviewers regarding the proposed indication #1: ----------(b)(4)----------
----------. There were issues related to the clinical trial design, risk-to-benefit assessment, and statistical analysis which raised questions about the significance of the reported difference in primary efficacy endpoint between treated and control arms.

An Information Request was sent to the Sponsor on 25 November 2009. Nycomed submitted their responses on 21 December 2009 which were mainly based on post-hoc analyses and did not demonstrate the link between the primary efficacy of TachoSil and direct clinical benefits to the patient for indication #1. During the teleconference on 22 January 2010, the Division informed Nycomed that the data did not support approval of the ---(b)(4)-- indication. ----(b)(4)----------
---------- indication -----(b)(4)----- and proceed with the hemostatic indication only.

The following Fibrin Sealant products are currently licensed by FDA: TISSEEL (Baxter Healthcare Corp.), ARTISS (Baxter Healthcare Corp.), CROSSEAL and EVICEL (OMRIX Biopharmaceuticals). These products are frozen solutions and lyophilized powder. TachoSil will be the first FDA-licensed Fibrin Sealant Patch.

Composition of TachoSil Fibrin Sealant Patch

Ingredient	Sponge Wt/cm^2 *Unit/cm^2*	Standard Size Wt/patch	Midi Size Wt/patch	Mini Size Wt/patch	Function Wt/patch	Reference to Standard
Active Ingredients						
Fibrinogen Active Substance (b)(4)						
Human Fibrinogen	5.5 mg	250.8 mg	126.5 mg	41.3 mg	Active Ingredient	
Albumin	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	Stabilizer	In-House

Sodium chloride	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	Excipients	
Sodium citrate	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-		
L-arginine hydrochloride	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-		
Human Thrombin						In-House
Human Thrombin	*2.0 IU*	*91.2 IU*	*46.0 IU*	*15.0 IU*	Active Ingredient	
Sodium chloride	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	Excipients	
Sodium citrate	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-		
Other Ingredients						
Riboflavin	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	colorant	-(b)(4)-
---(b)(4)---- ---------	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	--(b)(4)-- ---------	-(b)(4)-
---(b)(4)-- ----------	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	--(b)(4)-- ---------	-(b)(4)-
Equine Collagen Sponge	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	Mechanical support	-(b)(4)-

Optimal concentrations of Active Substances - Fibrinogen and Thrombin – were determined in two animal models as judged by ----------(b)(4)---------- ---------- ----------.

Upon contact with blood, other body fluids or saline solution, the coagulation factors in the TachoSil Patch are hydrated, and the subsequent fibrinogen-thrombin reaction initiates the last step of the coagulation cascade – formation of a viscous and elastic fibrin clot. Upon moistening, the Patch becomes pliable and extensible such that it can be molded to the affected tissue surface and can accommodate for the physiological movements of tissues and organs.

3. Chemistry, Manufacturing and Controls (CMC): Product and Facilities

Manufacture

The Manufacture of TachoSil Final Product includes the production of the Equine Collagen Sponge and the production of TachoSil Fibrin Sealant Patch, i.e., coating the collagen sponge sheets with a suspension of the Active Substances – Human Fibrinogen and Human Thrombin.

Brief Description of the Manufacturing Process

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Container Closure Integrity

Considering the hygroscopic properties of TachoSil, Nycomed provides a container closure system for TachoSil that consists of primary and secondary packaging. This double packaging system is used to protect the product against humidity, light, microbial ingress, foreign particles, and to maintain sterility after gamma irradiation, prior to patient use. The primary and secondary packaging for TachoSil is sized on the dedicated packaging line to fit each of the three TachoSil sizes (standard, midi, mini). The primary package is an inner blister pack with a single TachoSil sheet which can be of standard, midi or mini size. The inner or primary packaging manufactured by ----------(b)(4)----------, is a blister pack with a deep drawn tray made of gold lacquer polystyrene foil contact, sealed with a grid varnish coated (-(b)(4)-) medicinal paper on top. A vapor-proof secondary container is made of aluminum laminate foil. Sterilization of TachoSil is performed by gamma irradiation in the secondary packaging.

Sterilization Process

TachoSil final product is sterilized by gamma irradiation using gamma-rays from a -----(b)(4)---- based on the following:

---(b)(4)---

----------(b)(4)----------

Gamma irradiation is performed with ----------(b)(4)----------
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---. Thus, the actual dose is --------(b)(4)---------. The sterilization method and the sterilization dose have been used for the predecessor products - TachoComb, TachoComb H, TachoSil in Europe - for more than 15 years and not a single case of non-sterility has been observed.

Validation of Sterilization Process

The irradiation sterilization process of TachoSil was validated in two validation studies (Document 0903X-VB-0000008.01):

- A base validation study in 2008
- A re-validation study (auditing of sterilization dose of -(b)(4)-) in 2009

The validation included:

----------(b)(4)----------

----------(b)(4)----------

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----------(b)(4)----------

Thus, validation studies proved that the irradiation process is suitable for TachoSil and yields a sterile product with SAL of -(b)(4)- as required in -------(b)(4)------.

Manufacturing Sites

Name and Address	Responsibility
NYCOMED Austria GmbH, St. Peter Strasse 25, A-4020 Linz, Austria	Manufacture and packaging of TachoSil
----------(b)(4)----------	----------(b)(4)----------
NYCOMED Austria GmbH	Analytical testing (in-process, release, stability) except for Sterility, Pyrogen and General Safety testing
----------(b)(4)----------	----------(b)(4)----------
----------(b)(4)----------	-------(b)(4)--------

Assessment of Comparability of Licensed TachoSil EU and TachoSil Intended for the US Market

Comparative investigations were performed with the Active Substances – Human Fibrinogen and Human Thrombin, with the Coating Suspensions, as well as with the TachoSil products before (TachoSil IP) and after gamma irradiation (TachoSil Bulk).

Purity/Identity: Comparative ----------(b)(4)---------- under ----------(b)(4)---------- conditions demonstrated no differences in the ------(b)(4)------ between “EU” and “US” lots of Human Fibrinogen and Human Thrombin. Comparison of TachoSil “IP” and “Bulk” showed that ----------(b)(4)----------.

----------(b)(4)----------

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---(b)(4)--

In conclusion, TachoSil US is comparable to the commercial TachoSil EU. TachoSil EU has been on the European market since 2004 and has an acceptable safety profile.

Control of Starting Material

The Active Substances - Human Fibrinogen and Human Thrombin - contained in TachoSil US are supplied by --(b)(4)-- ---------------------------. Both Active Substances are manufactured from human plasma collected at FDA-licensed centers in the US. Both Human Fibrinogen and Human Thrombin are --(b)(4)-- controlled – Not More Than (NMT) ---(b)(4)--- for Thrombin and NMT ---(b)(4)--- for Fibrinogen. In addition, -------------------------------------(b)(4)------------------------------------ --- ---.

Horse tendons for production of Collagen Sponge are collected from slaughterhouses. ---(b)(4)-- (horse–(b)(4)) slaughterhouses are certified by authorities of the European Union. -----(b)(4)---- slaughterhouses possess an approval of the EU veterinary authorities and are listed on the FSIS (USDA) list as certified facilities. All slaughterhouses are regularly inspected and approved by the national veterinary authorities and are audited by Nycomed. Each batch of horse tendons supplied to Nycomed is accompanied by a veterinary certificate and by a QA certificate issued by a quality responsible person at the slaughterhouse.

Analytical Methods for Product Quality

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--(b)(4)---

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Final TachoSil Release Specifications (Standard Size)

Parameter	Limits		Analytical procedures
	Release	Shelf Life	
Appearance	Whitish sponge with one-side yellow coating	Whitish sponge with one-side yellow coating	visual
Length	----(b)(4)---	-	12237
Width	----(b)(4)----	-	12237
Adhesiveness of the coating	Abrasion -(b)(4)--------	Abrasion -(b)(4)--------	12238
Identification tests:			
Fibrinogen/Thrombin	Clot formation	-	12254
Riboflavin	Positive	-	12241
---(b)(4)---------- ----------	---------(b)(4)----- ----------	-	12242
Potency Assays:			
---(b)(4)---	---------(b)(4)---------- ---------	---------(b)(4)---------- ---------	12239
---(b)(4)----------	---------(b)(4)------	---------(b)(4)------	
---(b)(4)---	---------(b)(4)--------- ---------	---------(b)(4)--------- ---------	12240
---(b)(4)----------	---------(b)(4)------	---------(b)(4)------	
Fibrinogen/Thrombin	Clot formation within -(b)(4)- min	-	12254
Purity tests:			
---(b)(4)----------	---(b)(4)----	---(b)(4)----	---(b)(4)---
---(b)(4)---------- ----------	---(b)(4)----	-	12257
Abnormal Toxicity	Requirements according to -(b)(4)-	-	--(b)(4)--
Pyrogen Test	Requirements according to -(b)(4)-	-	---(b)(4)---
Microbiological test:			
Sterility (-(b)(4)- ----------)	sterile	Sterile (start and end of stability testing)	--(b)(4)---

Batch Analysis

Results of Batch Analyses are presented for TachoSil Bulk Validation Batches manufactured in 2008: Lots ----------(b)(4)---------- for Standard size; Lot ---(b)(4)-- for Midi size; and Lots ----------(b)(4)---------- for Mini size. Validation Lots were manufactured to validate the manufacturing process for TachoSil US.

Results of Batch Analyses are also presented for TachoSil Bulk Conformance Batches manufactured in January 2009: Lots ----------(b)(4)---------- for Standard size; Lot

----(b)(4)--- for Midi size; and Lots ----------(b)(4)---------- for Mini size. Conformance Lots were manufactured after implementation of the Change-over procedure between manufacture of TachoSil EU and TachoSil US.

Analytical data in the *Certificates of Analysis* are within the set Specification ranges for all Batches.

Stability Studies

Stability data include:

a) Pivotal Stability Data for -(b)(4)- Validation Lots manufactured in November 2007 with US-sourced fibrinogen and thrombin in the current commercial production area (-(b)(4)-----------):

   - 18 months stability data and SAS statistics for all ongoing storage conditions (2-8°C, 25°C/----------(b)(4)----------) and 6 months analytical and statistical data for storage condition at ------(b)(4)------

b) Stability Data for -(b)(4)- Conformance Lots manufactured in January 2009 with US-sourced fibrinogen and thrombin in the current commercial production area:

   - 9 months stability data (analytical) and SAS statistics for storage conditions at 2-8°C, 25°C/----------(b)(4)---------- and 6 months analytical and statistical data for storage conditions at ------(b)(4)-----

c) EU Primary and Secondary Supporting Stability Data for batches manufactured with -(b)(4)--sourced fibrinogen and thrombin in the current and previous commercial production areas, respectively:

   - -(b)(4)- months SAS statistics for storage conditions at 2-8°C, 25°C/--(b)(4)---------- and 6 months SAS statistics for storage condition at -----(b)(4)-----

For both the Conformance Lots and Validation Lots, all analytical stability data for reported periods are within Specification. There were no excursions or OOS data for any storage condition. There was no consistent trend for increase or decrease over time for fibrinogen, thrombin or ---(b)(4)----.

For the Validation batches, statistical analysis (based on the 18-months analytical data) supports the TachoSil shelf-life of 24 months for recommended storage conditions (at 2-8°C, 25°C/ ----------(b)(4)----------). For the Conformance Lots of standard size, based on the statistical projections from the 9-months analytical data at 5° ± 3° C, the shortest expiry dating was -(b)(4)- months for fibrinogen content; -(b)(4)- months based on thrombin content; and -(b)(4)- months based on -(b)(4)- content. Nycomed will continue to collect stability data and perform statistical analysis of the data for the Conformance Lots, and report the results in annual reports.

Evaluation of Safety Regarding Adventitious Agents

Viral Testing of Starting Material and Viral Clearance Steps in the Manufacturing Process for TachoSil

TachoSil contains, as Active Substances, Fibrinogen and Thrombin derived from human plasma. The risk that such products will transmit viruses has been reduced by the screening of plasma donors for prior exposure to certain viruses and by testing for the presence of current specific virus infections using FDA-licensed serological assays for HBV, HIV-1/2, HCV and nucleic acid testing (NAT) assays for HCV and HIV-1/2. Furthermore, the manufacturing process for Fibrinogen and Thrombin include pasteurization and precipitation and adsorption steps which have been validated in *in vitro* experiments and shown to be effective to inactivate and/or remove both enveloped and non-enveloped viruses ----------(b)(4)----------
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TachoSil contains a Collagen Sponge produced from equine tendons. The potential virus load of the tendons is considered low compared to blood or plasma. Step **(b)(4)** of the manufacturing process of the Collagen Sponge consists of ----------(b)(4)----------
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---.
Two studies (Study no. 2/01.105 in 2002 and Study no. 2/05.121 in 2006) were conducted (----------(b)(4)----------
---) to validate the inactivation of potential pathogenic viruses by -(b)(4)- pH treatment at pH -(b)(4)-. The results of the validation studies indicate that -(b)(4)- pH treatment is highly effective in the inactivation of enveloped viruses (Pseudorabies virus and Parainfluenza virus, with a LRF of ≥ 6 $\log_{10}$).

Finally, the product TachoSil is sterilized by gamma irradiation for --(b)(4)-- sterilization. Study no. 2/02.110 was conducted in 2002 to validate the gamma-irradiation step for its virus inactivation capacity. Gamma irradiation proved effective in the inactivation of enveloped viruses (Pseudorabies virus and Parainfluenza virus, LRF ≥ 4 $\log_{10}$) and non-enveloped moderately-resistant viruses relevant to the equine species (Reovirus Type 3 was used as a model virus for equine encephalosis virus, LRF ≥ 6 $\log_{10}$). Gamma irradiation was moderately effective in the inactivation of non-enveloped viruses with high resistance to physico-chemical treatments (Porcine Parvovirus, LRF of approximately 3 $\log_{10}$). However, cumulative viral clearance is higher (see Table 3 on p. 38)

The efficacy of gamma irradiation in sterilization was validated in two studies which demonstrated that the irradiation process is suitable for TachoSil and yields a sterile product with a Sterility Assurance Level of -(b)(4)- as required by ------(b)(4)------ (Please see section Validation of Sterilization Process).

Transmissible Spongiform Encephalopathy

TachoSil has an acceptable safety profile with regard to prions. TachoSil does not contain any bovine ingredients. According to current knowledge, horses do not develop prion disease. Measures to avoid cross contamination of the equine tendons are in place at the slaughterhouses. For the Active Substances - Human Fibrinogen and Human Thrombin - strict plasma donor selection criteria are employed by the manufacturer ----------(b)(4)----------
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Review of Manufacturing Facilities

Nycomed was founded in 1939. At present, it has 19 production sites distributed in 13 countries. The manufacturing facilities for TachoSil are located in Linz, Austria. The manufacture and packaging of TachoSil occurs on the -(b)(4)- floors of Building -(b)(4)-. These floors were added in 2004 ----------(b)(4)---------- to form the TachoSil Production Area. The TachoSil production area manufactures both TachoSil EU and TachoSil US. TachoSil US is coated with (b)(4) Human Fibrinogen (b)(4) and Thrombin for Further Manufacturing Use which are manufactured from human plasma collected at FDA-licensed centers. After manufacture of the fibrin sealant patch, the primary and secondary packaging of TachoSil is performed on the -----(b)(4)---------- which was renovated to allow for a dedicated TachoSil primary and secondary packaging suite when the ----(b)(4)--- floors were added. The packaged TachoSil collagen sheets are shipped to a contract ----------(b)(4)---------- for gamma irradiation ----------(b)(4)---------- and distribution from the ----------(b)(4)----------. Quality Control includes Laboratories for Biological Products; Laboratories for Pharmaceuticals; and Microbiological Laboratories which are located on the ----------(b)(4)----------, respectively. TachoSil will be Nycomed's first U.S. FDA-licensed product.

Inspection of the Manufacturing Facility

The Center for Biologics Evaluation and Research (CBER) performed a pre-license inspection for TachoSil (STN 125351/0 at Nycomed Austria GmbH facility in Linz, Austria, from December 10th to December 17th, 2009. This was the first FDA inspection of the TachoSil production area which was constructed in 2004 on the --(b)(4)-- floors of Nycomed's Building -(b)(4)-. The inspection included the complete manufacturing process for TachoSil which occurs on the ---(b)(4)--- floors of Building -(b)(4)-.

No inspectional observations were noted at the end of this pre-license inspection for TachoSil.

Environmental assessment

The BLA included a request from the applicant for a categorical exclusion for an Environmental Assessment as outlined in 21 CFR Part 25.31(a), (c) and 25.15(d). The FDA concluded that this request is justified, as the active ingredients of the proposed product are naturally occurring substances and no extraordinary circumstances, which would require an environmental assessment, exist.

General Conclusions

The manufacturing process was validated and ensures the reproducible manufacture of TachoSil at production scale. The review of the CMC information in this BLA demonstrated that the manufacturing process can consistently produce a product that meets predetermined quality attributes. In addition, the analysis of purity, identity and coagulation properties of the components of TachoSil, its clot formation characteristics and physiological sealing/gluing properties indicates comparability of the TachoSil products intended for the US market and that currently licensed in Europe. The manufacturing processes for Active Substances -(b)(4)- and Collagen Sponge at Nycomed as well as the sterilization of TachoSil Drug Product by gamma

irradiation provide acceptable safety margins regarding adventitious agents. The Product and Facility reviewers recommend approval of this BLA.

4. Non-clinical Pharmacology/Toxicology

Pharmacological/Toxicological Findings

TachoSil was determined to be safe for its intended use as a hemostat based on non-clinical studies (GLP and non-GLP) and its long-standing clinical history (outside of U.S.) and clinical studies in the U.S. in surgical settings. Pre-clinical studies consisted of a battery of studies to demonstrate the safety and effectiveness of TachoSil. Pre-clinical studies that were conducted to investigate toxicology, pharmacology (rats), efficacy (rats, mini-pigs, and -(b)(4)-), local tolerance (rabbits, mini-pigs, dogs, and pigs), antigenicity (guinea pigs, rats, and mini-pigs), limited immunogenicity (guinea pigs), and acute and repeat dose toxicity studies (mini-pig and dogs). The sponsor has completed a carcinogenic risk assessment analysis and limited studies to address potential long-term adverse effects from product use.

In pre-clinical studies, TachoSil was tested doses 5 to 7.5 fold the intended clinical dose (~2 standard size pads/surgery) for two weeks without any evidence of toxicity. Pharmacokinetic studies demonstrate that degradation of TachoSil begins within hours. Non-clinical studies also demonstrate that TachoSil immediately promotes the healing process. However, small remnants of TachoSil may be present up to 4 months after application (~5% of patch remaining in animal studies).

There was a safety concern regarding immunogenic responses to foreign components of TachoSil being introduced to patients when degradation of TachoSil occurs. This concern was raised by the equine origin of the collagen sponge (the main excipient of TachoSil) and the possibility that gamma irradiation may cause formation of neo-epitopes in active substances of TachoSil – Fibrinogen and Thrombin. This concern was conveyed by FDA to Nycomed in the 25 November, 2010 Information Request. The Sponsor's responses are summarized below.

1. Regarding equine origin of Collagen Sponge, sequence alignment of equine and human collagen (b)(4) proteins using the ----------(b)(4)----------
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   similarity) for alpha-1 and alpha-2 chains, respectively. High homology between human and equine proteins and high abundance of collagen (b)(4) I molecules itself makes it unlikely that humans will raise antibodies against the equine collagen contained in TachoSil.

   In animal studies, equine collagen was non-immunogenic in guinea pigs immunized by intraperitoneal insertion of a TachoComb patch (SR 103/28) or by application of non-coated equine collagen patch (Tachotop) into skin pockets on the contralateral sides of the back (SR UL/4829). This was judged by the lack of immunological reactions (erythema, inflammation or ulceration) up to 140 days after implantation. No antibodies to collagen were detected by the ---(b)(4)--- test.

   Equine collagen was immunogenic in guinea pigs only if animals were immunized with the -------(b)(4)------ of equine collagen and only in combination ----------(b)(4)----------
   ----------(SR UL/4830, ----------(b)(4)----------). No significant antibody

response was obtained in a clinically-relevant setting when a patch of equine collagen was implanted ----------(b)(4)----------. Equine collagen in the form of a TachoComb patch was well tolerated when repeatedly administered intraperitoneally in rats (SR 103/27).

2. The Study UL/5161 in rats investigated the potential formation of neo-epitopes in fibrinogen and thrombin induced by gamma irradiation. Animals were immunized by subcutaneous injection of native or gamma-irradiated fibrinogen or thrombin in solution with ----(b)(4)----------. No evidence of neo-epitope formation was revealed by ---(b)(4)----------. Antibody titers were determined by -(b)(4)- -----(b)(4)---------- on days 1, 11, 29, 40, 59, 73, 85 and 106, and were found comparable for both types of -(b)(4)-.

3. In a repeat-dose toxicity Study SR R-BP1270 in mini-pigs, TachoSil was topically applied to a liver wound on day 1 and 2 and the third patch was applied to the spleen wound on day 22. Immune response was assessed by a validated -(b)(4)-. Although low antibody titers were registered for equine collagen, human fibrinogen and human thrombin, they could not be unequivocally related to the use of TachoSil due to a high variability of antibody titers in pre-treatment samples. This result would be expected considering the foreign nature of human/equine proteins to the immune system of mini-pigs. Noteworthy, none of the mini-pigs revealed any evidence of systemic effects of antibodies leading to impaired hemostasis (assessed by thromboplastin time and partial thromboplastin time). ----------(b)(4)----------.

In conclusion, the results from pre-clinical studies indicate that TachoSil does not appear to be immunogenic and will not likely be anaphylactic. Further evaluation of immunogenicity of TachoSil will be performed in clinical studies conducted by Nycomed under an Investigational New Drug application (IND) ----------(b)(4)---------- indications for TachoSil. Therefore, no PMR/PMC to evaluate immunogenicity is required to support the approval of this BLA.

General Conclusions

Nycomed has completed an extensive non-clinical program to investigate the safety and effectiveness of TachoSil. Based on these findings, TachoSil was found to have an acceptable safety profile and was deemed suitable to initiate human studies. The Pharmacology/Toxicology Reviewer recommends approval of this BLA.

5. Clinical Pharmacology

Not Applicable

6. Clinical/Statistical

Review of Clinical Efficacy and Safety Data

Nycomed sponsored and completed a total of eleven clinical studies evaluating TachoSil as an adjunct to hemostasis. None of the clinical studies was conducted in the United States under Investigational New Drug applications. The outcome from Study TC-023-IM provides the pivotal efficacy data for this original BLA. Other studies: Studies ---------(b)(4)---------- and ---(b)(4)--- provide supportive data for safety.

Pivotal Study: Hemostatic Indication

Study TC-023-IM is the pivotal study that supports licensure of the TachoSil patch as an adjunct to hemostasis in cardiovascular surgery. This study was a Phase 3, multicenter, open-label, randomized, controlled trial comparing TachoSil and standard hemostatic fleece to evaluate the efficacy of TachoSil as an adjunct to hemostasis in cardiovascular surgery.

Randomization was done following the planned surgery and after achievement of primary hemostasis, when intra-operative bleeding had been assessed. Only patients with residual hemorrhage from the heart muscle, the pericardium, a major vessel or vascular bed requiring supportive hemostatic treatment were eligible for randomization. The intent-to-treat (ITT) dataset (n = 119) consisted of all randomized subjects. The primary and secondary efficacy endpoints were the proportion of patients with hemostasis at 3 minutes, and the proportion of patients with hemostasis at 6 minutes, respectively.

Efficacy Endpoint

The proportion of patients achieving hemostasis at 3 minutes after first application of the test treatment, was analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for center (data from small study centers were pooled). The Breslow-Day tests for homogeneity of the odds ratios across centers were omitted from the sub-group analysis due to small cell counts in many of the strata.

Efficacy results in cardiovascular surgery, by treatment, ITT population (n = 119)

Treatment	Total number of patients who achieved hemostasis	Proportion of patients who achieved hemostasis	95% CI for proportion[a]	p-value[b]
Hemostasis at 3 min				
TachoSil (n =59)	44	0.746	[0.635; 0.857]	< 0.0001
Comparator[c] (n=60)	20	0.333	[0.214; 0.453]	
Hemostasis at 6 min				
TachoSil (n =59)	56	0.949	[0.893;1.000]	< 0.0006
Comparator[c] (n=60)	43	0.717	[0.603; 0.831]	

[a] Normal approximation to the binominal distribution is used to construct the asymptotic confidence intervals
[b] Cochran-Mantel-Haenszel test controlling for center
[c] Hemostatic fleece material without additional active coagulation stimulating compounds

In the ITT population, subjects with missing time to hemostasis were counted in the group of subjects not having hemostasis at 3 minutes. For the per protocol (PP) population, missing time to hemostasis was left missing, *i.e.,* not included in the analysis.

Safety analysis from the Pivotal Cardiovascular Study

In the cardiovascular surgery adjunct to hemostasis study (TC-023-IM), adverse events (AEs) were reported in 46 patients (74.2%) treated with TachoSil and 43 patients (75.4%) treated with comparator treatment. The most commonly reported AEs in this study were atrial fibrillation and pleural effusion. There were no major differences in the distribution of AEs between the 2 treatment groups except for the occurrences of atrioventricular block, respiratory failure, decreased hemoglobin and wound infection which were slightly higher in the comparator group. These differences were not statistically significant.

Clinically Relevant Adverse Reactions Reported in at Least 5% of Patients in Either Treatment Group (cardiovascular study), Irrespective of Causality

Adverse Reaction (Preferred Term)	**TachoSil N = 62[2] n (%)**	**Comparator N = 57[2] n (%)**
At least 1 adverse event[1]	**46 (74.2%)**	**43 (75.4%)**
Atrial fibrillation	18 (29.0%)	14 (24.6%)
Pleural effusion	14 (22.6%)	11 (19.3%)
Hemorrhagic anemia	5 (8.1%)	6 (10.5%)
Tachyarrhythmia	4 (6.5%)	4 (7.0%)
Pyrexia	4 (6.5%)	3 (5.3%)
Pericardial effusion	3 (4.8%)	4 (7.0%)
Post procedural hemorrhage	3 (4.8%)	3 (5.3%)

[1] The table presents the number of patients experiencing at least 1 adverse reaction (regardless of causality. At each level of patient summarization, please note that a patient is counted once regardless of whether the patient had one or more events reported.
[2] As treated population (safety data set).

Supportive Safety Data from other Studies

During the clinical development of TachoSil, a total of 1038 patients were randomized in the 6 open-label, randomized, controlled clinical studies ----------(b)(4)---------- and TC-023-IM) included in the integrated data set (all studies data pool).

Pooled data from the hemostasis studies ----------(b)(4)---------- and TC-023-IM) included 544 patients randomly assigned and treated. Two hundred seventy-six patients (276) were treated with TachoSil and 268 received comparator treatment. Adverse events (AEs) were reported in 142 patients (51.4%) in the TachoSil group and 130 patients (48.5%) of the comparator group. There were 18 deaths from the adjunct-to-hemostasis studies included in the integrated safety database. There were 10 deaths [3.6%] in the TachoSil group and 8 deaths [3.0%] in the comparator group. In the cardiovascular surgery study (TC-023-IM), there were four deaths reported: 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 AEs with a fatal outcome were considered to be related to study treatment. All deaths were related to underlying illness or to complications of surgery.

In the studies of hemostasis, the pooled data show that 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 and not statistically significant.

Immunogenicity

Data from various TachoSil clinical studies did not raise immunogenicity concerns.

The clinical information regarding immunogenicity was assessed from: clinical study reports, survey of the AER (adverse event report) list and published studies:

- In 8 clinical studies, comprising 3,635 patients treated with TachoSil (830,000 fleeces), one patient (0.03 %) had a possible immunological event (pyrexia and eosinophilia) that was considered to be related to TachoSil. A detailed description of the event was not available, but it was not reported as serious.
- No allergic reactions were reported in 37 published studies on TachoSil.

----------(b)(4)----------

Efficacy and Safety Conclusions

Based on the results of the pivotal cardiovascular surgery study, the safety and efficacy of TachoSil have been demonstrated for the approved indication.

Orphan Product Designation

Not Applicable

Financial Disclosure Information

The sponsor reports financial disclosure information for many investigators at multiple sites. On the disclosure form, the sponsor acknowledged that they "have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)". They also certify that "each listed clinical investigator required to disclose to the sponsor whether the investigator had proprietary interest in the product or significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such interests". Nycomed further certified that "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)".

However, the sponsor also notes on page 22/22 (section 1.3.4 Financial certification and disclosure) that financial disclosure information was not obtained for several investigators at multiple sites. Nycomed states, "The reason for not having financial disclosure forms completed for all investigators is that the trials were not run under an IND, and therefore financial disclosure was not obtained for all investigators during the trial. The reason that we were not able to obtain financial disclosure forms after trial completion is that investigators have left the investigational sites, or that they are for other reasons not able to get in contact with despite repeated phone calls have been made to the sites concerned. Additionally, recommended letters

have been sent to investigators where financial disclosures are missing but only few have responded. None of the above investigators have indicated that they refused to complete a FDF (financial disclosure form) due to conflicts of interest."

Bioresearch Monitoring (BIMO)

Two (2) foreign clinical investigator inspections of Protocol TC-023-IM and one inspection of Protocol TC-019-IN were performed in support of the BLA under STN 125351/0 for TachoSil and were conducted in accordance with FDA's Compliance Program Guidance manual 7348.811, Inspection Program for Clinical Investigators.

Site#	Location	Number of Subjects Enrolled	Form FDA 483 Issued?	Inspection Final Classification
TC-019-IN-GBR013-01	Birmingham, UK	11	Y	OAI
TC023IM-DEU038	Leipzig, Germany	26	N	NAI
TC023IM-DEU039	Munchen, Germany	26	Y	VAI

NAI – No Action Indicated ; VAI – Voluntary Action Indicated ; OAI – Official Action Indicated

Summary Statement

The results of Bioresearch Monitoring inspections of Protocol **TC-023-IM** at two (2) foreign clinical investigator sites did not reveal problems that impact the data submitted in the application. This study provides the efficacy and safety data that support the indication of - adjunct to hemostasis in cardiovascular surgery in adults.

8. Pediatric Research Equity Act (PREA)

The pediatric studies have been deferred because the adult studies are completed and the results of the adult studies are adequate to support approval for the proposed indication. The Use in Specific Population Section of the label states, "The safety and effectiveness of TachoSil in pediatric patients undergoing cardiovascular surgery have not been established." Nycomed has submitted a pediatric plan for the deferred pediatric study: Use of TachoSil as an adjunct to hemostasis in pediatric patients 0-16 years undergoing hepatic surgery.

9. Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure is not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The mechanisms of action of fibrin sealants (fibrinogen/thrombin products) and their function in blood coagulation are well studied and understood.

- TachoSil is a fibrin sealant combination product derived from US sourced plasma that has been approved in Europe since 2004 where it has been used as an adjunct for hemostasis in surgery, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient.

- The results of the pivotal safety and efficacy study did not raise any major concerns related to safety and efficacy.

- Review of information submitted in the BLA for TachoSil did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendation.

10. Pharmacovigilance

Nycomed conducted an international, prospective, non-comparative cohort study entitled, "An international, non-interventional, prospective, single cohort study of the use of TachoSil in supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient." Existing data on all consenting subjects who had been treated with TachoSil during surgery by the participating physician were collected (i.e., no additional diagnostic procedures were performed). The subjects were observed for thromboembolic and immunological events, as well as drug interactions leading to thromboembolic events or major bleeding after exposure to TachoSil. In case of any such event, further information of the event and medical history was recorded by the participating physician.

The enrollment of 3,000 TachoSil treated patients was planned and 3,098 patients were included in the study. The primary endpoint was the proportion of patients experiencing a thromboembolic event verified by "paraclinical" (sponsor's verbatim term) examination. The total number and percentage of patients with a thromboembolic event following exposure to TachoSil were summarized with the associated 95% confidence interval. The following three adverse events categories were reported in the study:

- Thromboembolic Events
- Immunologic Events
- Major Bleeding Events

The thromboembolic and bleeding events were rare and not unexpected in these complex surgical populations. No specific immunologic monitoring was conducted during the clinical trials, and there is minimal clinical experience on re-exposure to TachoSil. One patient (0.03%) experienced at least one possible immunologic event during the study.

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; however, the viral transmission was unlikely related to TachoSil.

Nycomed's Proposed Pharmacovigilance Plan (PVP)

In addition to routine monitoring and reporting of spontaneously reported adverse events, Nycomed proposes the following Pharmacovigilance activities to monitor the post-approval use and safety of TachoSil in the US: review of spontaneous reports from health care professionals and lay persons, sponsor initiated, non-interventional post-authorization studies (see above), review of worldwide scientific literature, and review of post-authorization studies not sponsored by Nycomed. ----------(b)(4)----------
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11. Labeling

Proprietary Name

The Advertising and Promotional Labeling Branch (APLB) performed a re-evaluation of the proposed proprietary name, **TachoSil**, Fibrin Sealant Patch, to determine if any new products had been approved since the primary review dated 3 September 2009. APLB found that no products have been approved that would change their previous recommendation. APLB recommends that the proposed proprietary name TachoSil be found acceptable.

Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TachoSil safely and effectively. See full prescribing information for TachoSil.

TachoSil® (Absorbable Fibrin Sealant Patch)
Initial U.S. Approval: [20XX]

----------INDICATIONS AND USAGE----------
TachoSil is indicated as an adjunct to hemostasis for use in cardiovascular surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

Limitations of TachoSil Use
- Do not use TachoSil in the renal pelvis or near the ureter. (1.1)
- Do not use TachoSil in the closure of skin incisions. (1.1)
- Do not use TachoSil in neurosurgical procedures. (1.1)

----------DOSAGE AND ADMINISTRATION----------
Apply on the surface of tissue only. Do not use intravascularly. (2)
The number of TachoSil patches to be applied should be determined by the size of the bleeding area. (2)
Apply the **yellow, active side** of the patch to the bleeding area. (2)
Exposure to solutions containing alcohol, iodine or heavy metals may cause TachoSil to be denatured. (2.2)
Once removed from inner pouch, TachoSil cannot be resterilized. Discard unused, opened packages of TachoSil. (2.2)
Once TachoSil adheres, leave in place. If deemed medically necessary, use care to remove or reposition unattached patch. (2.2)
Do not exceed 7 patches sized 9.5 x 4.8 cm, 14 patches sized 4.8 x 4.8 cm,
or 42 patches sized 3.0 x 2.5 cm. (3, 5.5)

----------DOSAGE FORMS AND STRENGTHS----------
TachoSil is supplied in the following pack sizes (3):
- Package with 1 patch of 9.5 cm x 4.8 cm
- Package with 2 patches of 4.8 cm x 4.8 cm
- Package with 1 patch of 3.0 cm x 2.5 cm
- Package with 5 patches of 3.0 cm x 2.5 cm

Strength: TachoSil contains per cm^2: Human fibrinogen 3.6-7.4 mg (5.5 mg); Human thrombin 1.3-2.7 Units (2.0 U). (3)

----------CONTRAINDICATIONS----------
Do not apply TachoSil intravascularly. Intravascular application of TachoSil may result in life-threatening thromboembolic events. (4.1)
Do not use TachoSil in individuals with known hypersensitivity to human blood products or horse proteins. (4.2)

----------WARNINGS AND PRECAUTIONS----------

Do not use TachoSil in the treatment of severe or brisk arterial bleeding. (5.1)
Do not use TachoSil in place of sutures, ligature, cautery or other primary modes for control of hemostasis. (5.2)
Hypersensitivity or allergic/anaphylactoid reactions may occur with first-time or repetitive application of TachoSil (5.3)
Do not leave TachoSil in an infected or contaminated space. (5.4)
When placing TachoSil into cavities or closed spaces, exercise care to avoid over-packing. Use only the minimum amount of TachoSil patches necessary to achieve hemostasis. Unattached pieces of TachoSil should be carefully removed. (3, 5.5)
May carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agents, despite manufacturing steps designed to reduce the risk of viral transmission. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported in > 5% of patients were atrial fibrillation and pyrexia. Atrial fibrillation was reported in 6.1% of TachoSil cases (5.9% of controls) and pyrexia in 5.8% of TachoSil cases (4.9% of controls). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

_____USE IN SPECIFIC POPULATIONS_____

Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

TachoSil is indicated as an adjunct to hemostasis for use in cardiovascular surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

1.1 Limitations of TachoSil Use

- Do not use TachoSil in renal pelvis or ureter procedures because it may become potential foci for calculus formation.
- Do not use TachoSil in the closure of skin incisions because it may interfere with the healing of skin edges or cause wound dehiscence.
- Do not use TachoSil in neurosurgical procedures as safety and efficacy has not been evaluated in neurosurgery.

2. DOSAGE AND ADMINISTRATION

- **Apply on the surface of tissue only.** Do not use intravascularly.
- The number of TachoSil patches to be applied should be determined by the size of the bleeding area to be treated.
- Apply the **yellow, active side** of the patch to the bleeding area.
- Do not exceed 7 patches sized 9.5 x 4.8 cm, 14 patches sized 4.8 x 4.8 cm, or 42 patches sized 3.0 x 2.5 cm. (3, 5.5) (See Table 1 under (See DOSAGE FORMS AND STRENGTHS (3) and WARNINGS AND PRECAUTIONS, Closed Spaces (5.5)).

2.1 Preparation for Application of TachoSil patch

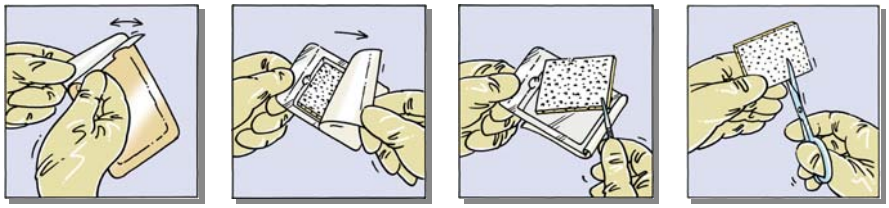
- TachoSil comes ready to use in sterile packages and must be handled accordingly. Use only undamaged packages as resterilization is not possible.

- When in the operating room, the outer aluminum foil pouch may be opened in a non-sterile environment (Fig. 1A). The **inner sterile blister must be opened in a sterile environment** (Fig. 1B).

- Remove the TachoSil patch from the blister (Fig. 1C), which can be used as a container for premoistening of the patch, if needed.

- Tailor the selection and application of TachoSil according to the size of the bleeding area. Select the appropriate TachoSil patch so that it extends 1 - 2 cm beyond the margins of the wound. The patch can be cut to the correct size and shape if desired (Fig. 1D). If more than one patch is used, overlap patches by at least 1 cm.

Figure 1: Pictures illustrating steps for preparation for application of TachoSil



A B C D

2.2 Method of Application

- Prior to application, cleanse the area to be treated to remove disinfectants and other fluids. The fibrinogen and thrombin proteins can be denatured by alcohol, iodine or heavy metal ions. If any of these substances have been used to clean the wound area, thoroughly irrigate the area before the application of TachoSil.

- Apply TachoSil directly to the bleeding area either wet or dry. If applied wet, pre-moisten TachoSil in 0.9% saline solution for no more than 1 minute and then apply immediately. In the case of a wet tissue surface (e.g., oozing bleeding) TachoSil may be applied without pre-moistening.

- Apply the yellow, active side of the patch to the bleeding area (Fig. 2A) and hold in place with gentle pressure applied through moistened gloves or a moist pad for **at least 3 minutes** (Fig. 2B).

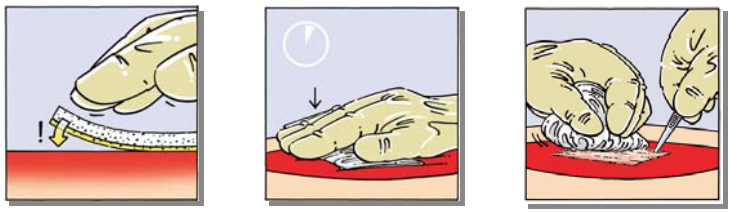
- When applying TachoSil, use precaution because the white, inactive side of TachoSil may also adhere to surgical instruments (e.g., forceps) or gloves covered with blood due to the affinity of collagen to blood. Pre-moisten surgical instruments and gloves with saline solution to reduce the adherence.

- After gently holding TachoSil to the bleeding area for **at least 3 minutes**, remove the gloved hand or moistened pad carefully from the patch. To avoid pulling the patch loose, first place a pre-moistened surgical instrument at one end of the patch before relieving the pressure (Fig. 2C). Gentle irrigation may also aid in removing the premoistened pad or glove hand without removing TachoSil from the bleeding area.

- Leave TachoSil in place once it adheres to organ tissue. Remove unattached TachoSil patches (or part of) and replace with new patches.

- TachoSil cannot be resterilized once removed from inner pouch. Discard unused, opened packages of TachoSil.

Figure 2: Pictures illustrating steps for method of application of TachoSil



A B C

For record-keeping purposes, record patient name and TachoSil batch number every time that TachoSil is administered to a patient.

3. DOSAGE FORMS AND STRENGTHS

Each patch is packaged in an appropriately sized blister pack of polystyrene formed foil and grid varnish coated medicinal paper and overwrapped with an aluminum laminate foil pack with a desiccant bag.

Each TachoSil patch is packaged individually and is supplied in the following pack sizes:

- Package with 1 patch of 9.5 cm x 4.8 cm
- Package with 2 patches of 4.8 cm x 4.8 cm
- Package with 1 patch of 3.0 cm x 2.5 cm
- Package with 5 patches of 3.0 cm x 2.5 cm

Strength: Each square centimeter of TachoSil contains:

Human fibrinogen	3.6 – 7.4 mg (5.5 mg)
Human thrombin	1.3 – 2.7 Units (2.0 U)

When applying TachoSil, do not exceed the maximum number of TachoSil patches shown in Table 1 (See WARNINGS AND PRECAUTIONS, Closed Spaces (5.5)).

Table 1

Amount of Fibrinogen and Thrombin per total patch size and maximum number of patches to be applied

TachoSil Patch Size	Amount of Human Fibrinogen/ Total Patch Size (mg)	Amount of Human Thrombin/Total Patch Size (Units)	Maximum Number of TachoSil Patches to be Applied
9.5 cm x 4.8 cm	337.4	123.1	7
4.8 cm x 4.8 cm	170.5	62.2	14
3.0 cm x 2.5 cm	55.5	20.3	42

Additional inactive ingredients: Equine collagen, human albumin, riboflavin (E 101), sodium chloride, sodium citrate, L-arginine hydrochloride.

4. CONTRAINDICATIONS

4.1 Intravascular Application

Do not apply TachoSil intravascularly. Intravascular application of TachoSil may result in life-threatening thromboembolic events (See ADVERSE REACTIONS, Post Marketing Experience (6.2)).

4.2 Hypersensitivity

Do not use TachoSil in individuals known to have anaphylactic or severe systemic reaction to human blood products or horse proteins (See ADVERSE REACTIONS, Post Marketing Experience (6.2)).

5. WARNINGS AND PRECAUTIONS

5.1 Arterial Bleeding

Do not use TachoSil for the treatment of severe or brisk arterial bleeding because TachoSil has not been evaluated in this treatment.

5.2 Primary Hemostasis

Do not use TachoSil as the primary mode to control hemostasis. TachoSil is not intended as a substitute for meticulous surgical technique and the proper application of suture, ligature or other conventional procedures for hemostasis.

5.3 Hypersensitivity/Allergic/Anaphylactic Reactions

Hypersensitivity or allergic/anaphylactoid reactions may occur with TachoSil. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. These reactions may occur in patients receiving TachoSil for the first time or may increase with repetitive applications of TachoSil.

In the event of hypersensitivity reactions, discontinue administration of TachoSil. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

5.4 Contaminated Spaces

Do not leave TachoSil in an infected or contaminated space because it may potentiate an existing infection.

5.5 Closed Spaces

When placing TachoSil into cavities or closed spaces, avoid over-packing because this may cause compression of underlying tissue. Use only the minimum amount of TachoSil patches necessary to achieve hemostasis (See DOSAGE FORM AND STRENGTHS (3)). Carefully

remove or reposition unattached pieces of TachoSil, if medically necessary (See DOSAGE AND ADMINISTRATION, Method of Application (2.2)).

5.6 Transmissible Infectious Agents

The active substances of TachoSil are made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain virus infections, and by inactivating and removing certain viruses (see DESCRIPTION, Viral Clearance (11)). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, telephone # 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection), immune-compromised individuals or individuals with an increased erythropoiesis (e.g. hemolytic anemia). (See USE IN SPECIAL POPULATIONS, Pregnancy (8.1) and PATIENT COUNSELING INFORMATION (17))

6. ADVERSE REACTIONS

The most common adverse reactions reported in > 5% of patients were atrial fibrillation and pyrexia. Atrial fibrillation was reported in 6.1% of TachoSil cases (5.9% of controls) and pyrexia in 5.8% of TachoSil cases (4.9% of controls).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the cardiovascular study the most frequently reported adverse reactions were atrial fibrillation (18 patients [29.0%] in the TachoSil group and 14 patients [24.6%] in the comparator group) and pleural effusion (14 patients [22.6%] in the TachoSil group and 11 patients [19.3%] in the comparator group), see Table 2.

Table 2
Clinically Relevant Adverse Reactions Reported in at Least 5% of Patients in Either Treatment Group (cardiovascular study), Irrespective of Causality

Adverse Reaction (Preferred Term)	TachoSil N = 62[2] n (%)	Comparator N = 57[2] n (%)
At least 1 adverse event[1]	**46 (74.2%)**	**43 (75.4%)**
Atrial fibrillation	18 (29.0%)	14 (24.6%)

Pleural effusion	14 (22.6%)	11 (19.3%)
Hemorrhagic anemia	5 (8.1%)	6 (10.5%)
Tachyarrhythmia	4 (6.5%)	4 (7.0%)
Pyrexia	4 (6.5%)	3 (5.3%)
Pericardial effusion	3 (4.8%)	4 (7.0%)
Post procedural hemorrhage	3 (4.8%)	3 (5.3%)

[1] The table presents the number of patients experiencing at least 1 adverse reaction (regardless of causality. At each level of patient summarization, please note that a patient is counted once regardless of whether the patient had one or more events reported.
[2] As treated population (safety data set).

6.2 Post Marketing Experience

The following adverse reactions have been reported in post marketing experience with TachoSil in the EU and could reasonably be expected to occur with TachoSil in the US:

General disorders and administration site conditions: drug ineffective, inflammation, granuloma, catheter related complication, multiorgan failure, pyrexia

Injury, poisoning and procedural complications: post procedural hemorrhage, foreign body trauma, post procedural pulmonary embolism

Vascular disorders: phlebitis, hematoma, hemorrhage, thrombosis

Infections and infestations: hepatitis C, abscess

Respiratory, thoracic and mediastinal disorders: respiratory distress, laryngeal edema, hemothorax

Blood and lymphatic system disorders: splenic hemorrhage, eosinophilia

Hepatobiliary disorders: biloma, portal vein thrombosis

Renal and urinary disorders: renal artery thrombosis, renal failure

Endocrine disorders: parathyroid disorder

Eye disorders: mydriasis

Nervous system disorders: nerve compression

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7. DRUG INTERACTIONS

No drug interactions are known.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with TachoSil. There are no adequate and well-controlled studies in pregnant women. It is also not known whether TachoSil can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Some viruses, such as parvovirus B19, are particularly difficult to remove or

inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection). TachoSil should be administered to pregnant women only if clearly needed (see PATIENT COUNSELING INFORMATION (17)).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TachoSil is administered to nursing mothers.

8.4 Pediatric Use

The safety and effectiveness of TachoSil in pediatric patients undergoing cardiovascular surgery have not been established.

8.5 Geriatric Use

Clinical trials included 219 patients older than 65 years of age receiving TachoSil. No overall differences in safety or effectiveness were observed between the elderly and younger patients. However, greater susceptibility of some older patients to adverse reactions cannot be ruled out.

11. DESCRIPTION

TachoSil is a fibrin sealant patch consisting of an off-white, closed cell, equine collagen sponge coated on one side with two active ingredients: human fibrinogen and human thrombin. Riboflavin is included in the coating mixture as a yellow colorant to signify the active surface. Each square centimeter contains approximately 5.5 mg of human fibrinogen and 2.0 units of human thrombin. Other inactive ingredients include equine collagen, human albumin, sodium chloride, sodium citrate and L-arginine hydrochloride.

Each patch is packaged in an appropriately sized blister pack of polystyrene formed foil and grid varnish coated medicinal paper and overwrapped with an aluminum laminate foil pack with a desiccant bag.

Viral Clearance

The manufacturing procedure of TachoSil and its active substances Fibrinogen and Thrombin includes processing steps designed to reduce the risk of viral transmission. In particular, pasteurization, precipitation and adsorption steps are included in the manufacturing of Fibrinogen and Thrombin and pH treatment in the manufacturing of Collagen Sponge.

Validation studies for Fibrinogen and Thrombin and Collagen Sponge manufacturing steps were conducted for their capacity to inactivate and/or remove viruses. These in vitro validation studies were conducted, using samples from manufacturing intermediates spiked with virus suspensions of known titers followed by further processing under conditions equivalent to those in the respective manufacturing steps. The cumulative virus reduction factors (expressed as $\log_{10}$) are shown in Table 3 for each virus tested.

TachoSil is sterilized by gamma irradiation after completion of inner and outer packaging, resulting in a sterile product in a sterile inner package. A validation study was conducted evaluating the capacity of gamma irradiation to inactivate viruses. The virus reduction factors (expressed as $\log_{10}$) for the final sterilization of TachoSil by gamma irradiation are shown in Table 4 for each virus tested.

Table 3

Cumulative virus reduction factors for the components of TachoSil

Cumulative Reduction Factors for Virus Removal/Inactivation of Human Thrombin					
	Reduction Factors [$\log_{10}$] of Virus[1] tested				
Manufacturing step	HIV-1	HSV	BVDV	CPV	HAV
Pasteurization, precipitation and adsorption steps	≥ 19.6	≥ 21.4	≥ 13.4	6.6	8.7
Cumulative Reduction Factors for Virus Removal/Inactivation of Human Fibrinogen					
	Reduction Factors [$\log_{10}$] of Virus[1] tested				
Manufacturing step	HIV-1	HSV[2]	BVDV	CPV	HAV
Pasteurization, precipitation and adsorption steps	≥9.6	≥ 9.1	≥ 11.2	4.4	≥ 6.7
Reduction Factors for Virus Removal/Inactivation of the Collagen Sponge (equine)					
	Reduction Factors [$\log_{10}$] of Virus[1] tested				
Manufacturing step	PRV	PI-3	PPV	Reo3	
pH treatment	≥ 5.7	≥ 5.9	---	---	

[1] HIV-1: Human Immunodeficiency Virus 1
HSV: Herpes Simplex Virus
BVDV: Bovine Viral Diarrhoea Virus
HAV: Hepatitis A Virus
PRV: Pseudorabies Virus
PI-3: Parainfluenza Virus type 3
PPV: Porcine Parvovirus
Reo 3: Reo Virus type 3

[2] Additional reduction factor [log10] of 1.6 for PRV not included in cumulative reduction factor for HSV

Table 4

Virus reduction factors for the final sterilization by gamma irradiation

Reduction Factor of Gamma Irradiation (Final Sterilization of TachoSil)				
	Reduction Factors [$\log_{10}$] of Virus[1] tested			
Manufacturing step	PRV	PI-3	PPV	Reo3
Gamma Irradiation	≥ 4.7	≥ 4.0	3.0	≥ 6.2

[1] PRV: Pseudorabies Virus

PI-3: Parainfluenza Virus type 3
PPV: Porcine Parvovirus
Reo 3: Reo Virus type 3

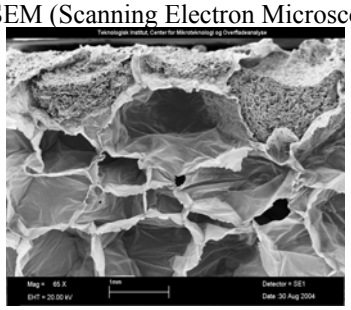
All infections considered by a physician possibly to have been transmitted by this product should be reported to Baxter. (See WARNINGS AND PRECAUTIONS, Transmissible Infectious Agents Infection Risk from Human Plasma (5.36))

12. CLINICAL PHARMACOLOGY

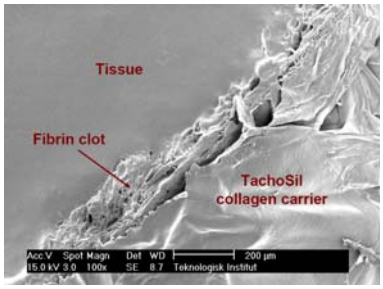
12.1 Mechanism of Action

TachoSil contains human fibrinogen and human thrombin as a dried coating on the surface of an equine collagen patch (Fig. 3A). When TachoSil is in contact with physiological fluids, the components of the coating dissolve and partly diffuse into the wound surface. Soluble fibrinogen is transformed into fibrin, by the enzymatic action of thrombin, which polymerizes into a fibrin clot that adheres the collagen patch to the wound surface and achieves hemostasis (Fig 3B). TachoSil exhibits flexibility to accommodate for the physiological movements of tissues and organs and can withstand pressures up to 61.4 hPa (46.1 mm Hg).

Figure 3: SEM (Scanning Electron Microscopy) photos of TachoSil



A. This side view of the TachoSil patch shows the coating of the human plasma components anchored to the indentations of the collagen carrier.



B. The deposition of a fibrin clot formed from the fibrinogen and thrombin of the coating causes hemostasis and conglutination of the TachoSil patch to the tissue wound.

In animal studies, TachoSil progressively biodegrades with only a few remnants left after 13 weeks. After complete biodegradation, no remnants of the TachoSil patch remained in the body.

12.2 Pharmacodynamics

Clinical studies demonstrating hemostasis were conducted in a total of 119 patients undergoing cardiovascular surgery. Efficacy data is provided in section 14.

12.3 Pharmacokinetics

Pharmacokinetic studies have not been performed. Because TachoSil is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of TachoSil or studies to determine the genotoxicity or the effect of TachoSil on fertility have not been performed.

14. CLINICAL STUDIES

An open-label, multicenter, 1:1 randomized, parallel-group study comparing TachoSil with comparator (hemostatic fleece without additional active coagulation stimulating compounds) treatment was conducted to evaluate TachoSil for control of bleeding in 119 patients undergoing cardiovascular surgery requiring cardiopulmonary bypass procedure.

In the Intention to Treat (ITT) population (119 patients), 59 patients were treated with TachoSil and 60 patients were treated with the comparator. A larger proportion of patients in the TachoSil treatment group (44/59; 74.6%) than in the comparator treatment group (20/60; 33.3%) achieved hemostasis within 3 minutes, which was a statistically significant difference ($p<0.0001$, CMH test controlling for center). Fifty-six out of 59 (94.9%) patients in the TachoSil treatment group achieved hemostasis at 6 minutes compared to 43 out of 60 (71.7%) in the comparator treatment group, which was statistically significant ($p=0.0006$, CMH test controlling for center), see Table 5.

Table 5

Efficacy results in cardiovascular surgery, by treatment, ITT population (n = 119)

Treatment	Total number of patients who achieved hemostasis	Proportion of patients who achieved hemostasis	95% CI for proportion[a]	p-value[b]
Hemostasis at 3 min				
TachoSil (n =59)	44	0.746	[0.635; 0.857]	< 0.0001
Comparator[c] (n=60)	20	0.333	[0.214; 0.453]	
Hemostasis at 6 min				
TachoSil (n =59)	56	0.949	[0.893;1.000]	< 0.0006
Comparator[c] (n=60)	43	0.717	[0.603; 0.831]	

[a] Normal approximation to the binominal distribution is used to construct the asymptotic confidence intervals
[b] Cochran-Mantel-Haenszel test controlling for center
[c] Hemostatic fleece material without additional active coagulation stimulating compounds

16. HOW SUPPLIED/STORAGE AND HANDLING

Each patch is packaged in an appropriately sized blister pack of polystyrene formed foil and grid varnish coated medicinal paper and overwrapped with an aluminum laminate foil pack with a desiccant bag. Each patch is packaged individually.

TachoSil is supplied in the following pack sizes:

- Package with 1 patch of 9.5 cm x 4.8 cm (NDC 0944-XXXX-XX)_

- Package with 2 patches of 4.8 cm x 4.8 cm (NDC 0944-XXXX-XX)_
- Package with 1 patch of 3.0 cm x 2.5 cm (NDC 0944-XXXX-XX)_
- Package with 5 patches of 3.0 cm x 2.5 cm (NDC 0944-XXXX-XX)_

Storage

TachoSil should be stored between 2ºC and 25ºC.

TachoSil does not require refrigeration. Do not freeze.

17. PATIENT COUNSELING INFORMATION

Advise patients that, because TachoSil is made from human blood, it may carry a risk of transmitting infections agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent (See WARNINGS AND PRECAUTIONS, Transmissible Infectious Agents (5.86) and DESCRIPTION (11)).

Instruct patients to consult their physician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain (see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)).

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Manufactured by:
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12. Recommendation

Approval