



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: July 30, 2009

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch,
Division of Hematology, OBRR

SUBJECT: STN 125351 Nycomed BLA for TachoSil filing memo

SPONSOR: Nycomed

TO: Nisha Jain, MD, Acting Chief, Clinical Review Branch

CC: Natalya Ananyeva, PhD, visiting scientist, OBRR/DH/LH
Jie He, Regulatory Project Manager, OBRR/DBA/RPMB

Recommendation: Preliminarily, from a clinical review discipline the BLA is filable with additional requests for information.

Information requests:

As per discussions with Chunrong Cheng, biostatistician assigned to review the BLA, we should request the following information:

1. Please submit the complete datasets (i.e. SAS transport files) from the following studies to permit a full safety evaluation: -----(b)(4)-----.
2. It has been noted that the datasets were submitted in the AdAM format, which is currently not supported or being accepted by CBER. As per telephone call to the sponsor on Monday August 3, 2009, we are requesting that the sponsor provide the corresponding SAS program files using the .sas extension for the individual analysis of studies -----(b)(4)-----.
3. Please submit a label in the SPL format.
4. Please clarify if study TC-019-IN is intended to address US. Regulatory PREA requirements.

Additional clinical information requests may be made as the review process continues.

Background:

TachoSil is a ready to use degradable surgical patch developed for topical use to support intraoperative hemostasis -----(b)(4)-----.

The TachoSil patch consists of a dry -(b)(4)- collagen material made from equine tendons, coated with human fibrinogen and human thrombin. This fixed combination is intended to be applied topically to the wound surface and can be left *in situ*. Upon contact with blood, body fluids or normal saline, the components of the coating dissolve, diffuse partly into the wound surface and are activated. The clotting process involving polymerization of fibrin monomers and crosslinking takes about 3-5 minutes. TachoSil must be pressed onto the wound area. The components of TachoSil are degraded enzymatically and by phagocytosis in approximately -(b)(4)- months post application.

The present BLA 125351 is the first regulatory submission for marketing approval of TachoSil in the United States. The contents of the BLA are intended to support the following indications:

- -----(b)(4)-----
- TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery
- -----(b)(4)-----

TachoSil was first approved by the European Commission on June 8, 2004 for supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient. The product has obtained marketing authorizations in 42 countries and is marketed in 30 countries outside the United States.

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Clinical Development Program

TachoSil was initially developed with the name TachoCombS. TachoSil has two predecessor products TachoComb and TachoComb H, both of which contained aprotinin. TachoComb and TachoComb H were marketed in Europe at the time that marketing authorization was obtained for TachoComb S (June 2004).

A total of 11 clinical studies sponsored by Nycomed have been completed, of which 3 provide pivotal data intended to support the indications sought in this BLA. Seven of the studies are intended to provide efficacy and safety data for the BLA. Six (6) of these studies were controlled and 1 was an uncontrolled pediatric study. An additional four (4) uncontrolled studies are intended to provide additional safety data.

The following table lists the individual completed studies of the TachoSil clinical development program.

Table 1: Completed Clinical Studies on TachoSil

	Surgical indication	Study Code	Treatments ^a	N	Study Period
Controlled studies providing safety and efficacy data					
1	(b)(4)		TS vs standard surgical treatment	189	2000-2002
2			TS vs standard surgical treatment	301	2006-2007
3	Cardiovascular surgery	TC-023-IM	TS vs hemostatic fleece	120	2006-2007
Controlled studies providing safety data and supportive efficacy data					
4	(b)(4)			121	2001-2002
5				188	2002-2004
6				119	2003-2003
Uncontrolled studies providing additional safety and efficacy ^b data					
7	Liver resection (children)	TC-019-IN	TS (no comparator)	16	2006-2007
8	Various surgeries	TC-018-IN	TS (no comparator)	3098	2005-2008
9	(b)(4)		TS (no comparator)	154	2004-2005
10			TS (no comparator)	616 ^c	2005-2007
11			TS (no comparator)	169	2007-2008

^a TS, TachoComb S or TachoSil.

^b Efficacy data from the pediatric study TC-019-IN.

^c 324 patients received treatment with TachoSil.

Three additional studies are currently ongoing, one of which is under the sponsorship of -
----- (b)(4) -----.

Table 2: Ongoing Clinical Studies on TachoSil

	Surgical indication	Study Code	Treatments ^a	N (planned)
12	(b)(4)		TS vs TachoComb®	100
13			TS (no comparator)	30
14			TS (no comparator)	500

^a TS, TachoSil.

The studies were conducted in the European Economic Area except study (b)(4)

According to the sponsor, the outcome of study --(b)(4)-- will prove to be critically important in terms of later clinical development of TachoSil in -----(b)(4)-----.
Nycomed further plans to -----(b)(4)-----

------(b)(4)----- . These studies are planned to be conducted solely in the US with the purpose of -----(b)(4)----- . Furthermore, a ----(b)(4)---- study evaluating the use of TachoSil in ----(b)(4)---- is planned for conduct the US and Europe.

The BLA contains the following 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 elective (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 elective (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) 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) fibrin sealants, poly-saccharides, collagen fleece, others)	TachoSil Topical, intraoperative Application	616	Patients undergoing (b)(4) 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 (b)(4)	Prospective, noninterventional, open-label cohort study	TachoSil Topical, intraoperative Application	160	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 (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						

The BLA contains raw STDM datasets and analysis dataset for the pivotal studies intended to support the requested indications: -----(b)(4)-----, TC-023-IM, -(b)(4)-

Study TC-018 IN and TC-019-IN have only tabulated datasets. These are intended only to evaluate safety. TC-019-IN is the observational study in pediatric patients that was requested by the European regulatory authorities.