

Mid-Cycle Meeting Summary for BLA 125351/0; DATS466198 - TachoSil, November 20, 2009

MEMORANDUM

MEETING DATE: 10 November 2009 (face-to-face)
MEMO DATE: 20 November 2009
FROM: Jie He
Natalya Ananyeva
TO: File BLA 125351/0; DATS466198
RE: Mid-Cycle Meeting Summary for BLA 125351/0; DATS466198

BACKGROUND

This is an original BLA application for Fibrin Sealant Patch (FDA-recommended name) submitted by Nycomed, Denmark on June 5, 2009. The proposed trade name is TachoSil. Fibrin Sealant Patch is a ready-to-use fibrin sealant product where two Active Substances - Human Fibrinogen and Human Thrombin – are coated onto a Collagen Sponge. TachoSil is a combination product where the Collagen Sponge is classified as a Medical Device. The Collagen Sponge serves as a flexible and mechanically-stable carrier. Human Fibrinogen Active Substance and Human Thrombin Active Substance are supplied to Nycomed by -----(b)(4)-----

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Proposed indications for TachoSil:

BLA 125351/0 was filed on August 3, 2009

ATTENDEES:

Tim Lee	Acting Chief of Laboratory of Hemostasis, DH, OBRR
Jie He	RPM
Natalya Ananyeva	Chairperson, CMC reviewer
Laura Wood	CMC reviewer
La’Nissa Brown	Pharmacology/Toxicology reviewer
Kimberly Lindsey	Clinical reviewer

Chunrong Cheng	Statistical reviewer
Martha O'Lone	DMPQ reviewer
Lillian Ortega	BIMO
Jean Makie	DCM/APLB

AGENDA:

The Meeting was focused on discussion among reviewers of all disciplines on the status of the review of BLA 125351/0 and identified issues with the submitted data.

Specifically:

CMC

The overall description of the pharmaceutical development, manufacturing process and characterization of Fibrin Sealant Patch "TachoSil" seem acceptable at this time.

The following issues need to be addressed through Information Request:

1. Equine nature of the Collagen Sponge and the possibility that gamma-irradiation may cause formation of neo-epitopes in Active Substances of TachoSil raise a potential safety concern with regard to immunogenicity of the product. The protocol for validated immunogenicity assays for monitoring -----(b)(4)----- and determination of -----(b)(4)---- should be requested from Nycomed. -----
------(b)(5)-----
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2. Updated stability data (both analytical and SAS statistics) for Validation (manufactured in November 2007) and Conformance Lots (manufactured in January 2009) of TachoSil should be requested.
3. Justification should be requested to support the set ------(b)(4)----- as sufficient to prevent -----(b)(4)----- fibrinogen and to support consistency of determination from lot to lot.
4. Regarding viral inactivation/reduction studies, the cumulative virus reduction factors for Active Substances of TachoSil should be corrected.

Detailed comments to the Sponsor will be provided in the Information Request.

CDRH

The CDRH consult was requested on July 7, 2009. Peter Hudson was not present at the meeting due to illness.

Pre-Clinical

The varying sizes/doses of fibrin sealant patch (mini, standard, midi) and the possibility of multiple use of the product constitute additional safety concerns in terms of potential adverse events (infection, thrombogenicity, immunogenicity, carcinogenicity). Considering a long resorption period of TachoSil (-(b)(4)- months), the submitted preclinical data assessing long-term safety of TachoSil after implantation appear insufficient. Detailed comments to the Sponsor will be provided in the Information Request. The reviewer advised that these concerns can be evaluated and monitored under PMC.

Clinical, Statistical

The results of pivotal studies were discussed.

1. Major deficiencies were found with Indication #1 (------(b)(4)-----). Specifically, there are issues with Risk-to-Benefit assessment (reported Primary Efficacy is questionable and is only -(b)(4)- hour- difference in comparison with control); Clinical Trial Design (clinical center effect, no stratification); Safety assessment (lack of an algorithm in monitoring infections or immunogenicity); statistical issues (significance of the reported difference in efficacy is questionable). Detailed comments to the Sponsor will be provided in the Information Request. More time is needed to review the complete submission. -----
------(b)(5)-----
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2. For indication #2 (Adjunct to hemostasis in cardiovascular surgery), it is potentially approvable; however further review is needed.
3. PREA has not been specifically addressed by the sponsor. The Sponsor should formally ask for pediatric deferral for both indications.

BIMO

Inspections of 6 study sites have been scheduled. The requested completion date for the inspection is January 15, 2010.

RPM

Nycomed has the option to withdraw one of the indications that FDA deems not ready to be approved, and the FDA would continue to review the reminder of the submission. Alternatively, a Complete Response letter for the entire BLA would be issued. FDA can not approve a portion of the BLA.

DMPQ

1. Pre-license Inspection is scheduled for the period of December 10-18th, 2009.
2. It was clarified for the Review Committee that the Action Due date for Nycomed BLA should coincide with Action Due dates for -----(b)(4)-----
----- for TachoSil Patch and can not be approved as stand-alone files. Thus, Action Due date for Nycomed (April 5, 2010 currently listed in all documents) should be moved to March 29, 2010 ----(b)(4)-----.
3. For the Information Request, the following DMPQ questions should be included:
 - **Raw Materials/Reagents:**
 - a. Please provide more information on the incoming requirements for your equine materials and describe in detail any testing that is performed and results of that testing.
 - b. Please provide validation data for freedom of adventitious agents.
 - c. Please describe any incoming endotoxin and bioburden limit specifications and testing performed for components and materials on receipt.
 - **Cleaning:** Please provide a justification for the use of ----(b)(4)---- as a cleaning agent for removal of potential prion contamination.
 - **Release Criteria:** What are the endotoxin limits on the final finished product? Please provide data on how these limits are tested and the results of that testing.
 - **Change in equipment used for -----(b)(4)----- of coating suspension:** Section 3.2.P.2.3, Pharmaceutical Development of Manufacturing process, page 10 states

that the ---(b)(4)--- device for the preparation of the fibrinogen suspension was changed from -----(b)(4)----- . Please clarify the currently used ---(b)(4)--- device since the former ---(b)(4)--- device is stated in the major process equipment list (section 3.2.A.1, page 14).

APLB

Upon primary review, the Advertising and Promotional Labeling Branch finds the proposed proprietary name TachoSil acceptable (**Review Memo dated September 3, 2009 in EDR**). It is too early to have secondary review at this point.

Pharmacovigilance reviewer was assigned

Faith Barash, MD MPH

Therapeutics and Blood Safety Branch

Division of Epidemiology, Office of Biostatistics and Epidemiology

CBER, FDA

301-827-6081

Tentative strategy for further review

- Submit detailed Information Request for the identified issues ASAP
- Currently, two options were suggested by the Review Committee: (i) advise the Sponsor to de-couple two indications, i.e. -----(b)(4)----- with indication #2 (Adjunct to hemostasis in cardiovascular surgery) OR (ii) issue CR for the whole BLA **after review of BLA is completed**. How these options should be communicated to the Sponsor is being discussed.

1. -----(b)(4)-----
2. Adjunct to hemostasis in cardiovascular surgery