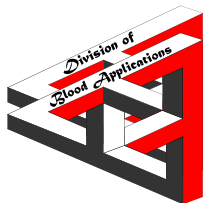


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FACSIMILE TRANSMISSION RECORD
Division of Blood Applications
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November 25, 2009

FAX No. 919-654-0626

To: Ms. Camilla Wamberg, Nycomed Danmark ApS

Our Reference No: BL 125351/0

Nycomed Danmark ApS
Attention: Ms. Camilla Wamberg
Langebjerg 1
DK-4000 Roskilde
Denmark

Dear Ms. Wamberg:

We are reviewing your Biologics License Application (BLA) dated June 3, 2009, including amendments dated July 2, September 2, 21, and October 1, 2009, for the Fibrin Sealant Patch and have determined that the following information is necessary to take complete action. Please submit your written response to the following items so that we can continue evaluating your BLA.

Clinical

1. -----(b)(4)-----

 - a. -----(b)(4)-----

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2. -----(b)(4)-----

Two (2) Pages Determined to be Non-Releasable: (b)(4)

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11. -----(b)(4)-----

12. -----(b)(4)-----

Pediatric Research Equity Act (PREA) requirements

13. With respect to study TC-019-IN, the pediatric observational study in liver transplantation, you intend to satisfy the PREA requirements for the hemostatic indication. It is our determination that this study, which was terminated prematurely, is neither sufficient to support the pediatric labeling nor is it sufficient to meet the PREA requirements for TachoSil. You did not address the PREA requirements formally in the BLA submission; therefore, we request that you formally submit pediatric deferral requests for both the -(b)(4)- and hemostatic indications.

Pharmacovigilance

14. Please submit a pharmacovigilance plan for the BLA according to ICH guidance E2E.

Immunogenicity

15. The equine origin of the collagen sponge and the possibility that gamma irradiation may cause formation of neoepitopes in active substances of TachoSil raise a potential safety concern.
- a. You conducted several preclinical toxicity and immunogenicity studies using TachoSil and its predecessors or individual components of the fibrin sealant patch. These studies contain major deficiencies. Specifically, the studies lack systematic evaluation of relevant immunogenic endpoints that should include, but not be limited

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to, antibody formation (neutralizing, cross-reacting, etc.), relevant time points after exposure to the product, dosing at toxic levels (after establishing the Maximal Tolerated Dose, MTD), etc. Please comment.

16. You identified clinical assessments to include pyrexia, rash, pruritus, eosinophilia and increased white blood cell count as evidence of immunological reactions. Our major clinical concern regarding potential immunogenicity of TachoSil, however, is predicated on the possibility that TachoSil usage will result in the development of antibodies (neutralizing and non-neutralizing antibodies) against thrombin and fibrinogen or equine collagen that would lead to decreased efficacy of the product and possible bleeding complications. This concern is also based on the slow rate of resorption of the TachoSil Patch (-(b)(4)- months) and the possibility of presence of a considerable amount of -----(b)(4)----- thrombin due to initial ----(b)(4)---- of thrombin and losses during the manufacturing process.

In our pre-BLA discussions, we requested that you assess immunogenicity of your product. We did not see a prospective plan incorporated in your clinical protocols (in particular, pivotal studies TC-023-IM and -(b)(4)--IM intended to support initial US licensure) to monitor the formation of antibodies to thrombin, fibrinogen or collagen. You should assess immunogenicity with biochemical laboratory parameters in conjunction with clinical parameters.

- a. Please provide the protocol for sensitive validated immunogenicity assays for monitoring antibody formation and determination of antibody titers (e.g. ELISA) you will use in the clinical studies evaluating safety and efficacy of TachoSil. You should validate the method(s) according to ICH guidelines Q2A and Q2B. Please note that the time intervals for blood collection must correlate with the physico-chemical resorptive properties of TachoSil.

Pharmacology/Toxicology

17. The various sizes/doses of the fibrin sealant patch (standard, midi, mini) constitute an additional safety concern that will need to be evaluated and monitored to determine the correlation, if any, between potential adverse events and increased dosing and multiple use of the product. Therefore:
- a. Please submit either preclinical or clinical data that support the maximal amount (size/dose) of TachoSil patch that can remain *in situ*.
- b. Please submit either preclinical or clinical data that support repeated use of TachoSil.
18. Insufficient preclinical data that assess long-term safety following TachoSil implantation after complete resorption and degradation of the product have been submitted in the BLA.

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- a. You claim that complete resorption period is -(b)(4)- months; therefore safety assessments should at least cover the duration of complete product resorption. Please submit either preclinical or clinical data with the observation period of the product up to 6 months after application and implantation to thoroughly evaluate its long-term safety.
- b. Please submit a toxicological risk assessment to investigate the potential carcinogenic risk following implantation with TachoSil and its components. Data from literature, nonclinical and clinical studies, database searches and any other pertinent information should be evaluated to address this potential.

CMC

19. Regarding the viral inactivation/reduction table for Fibrinogen Active Substance -(b)(4)- (Table 3.2.A.2.3.2-1):

- a. -----(b)(4)-----

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

20. As indicated in the correspondence of 22 October 2009, please submit updated stability data for three TachoSil Conformance Lots that have been stored up to 9 months under the $5^{\circ} \pm 3^{\circ} \text{C}$, 25°C /------(b)(4)----- storage conditions, and up to 6 months at -----(b)(4)-----
----- Also, please provide updated stability data for the three Validation Lots.

21. Please provide more detailed justification for the development of -----(b)(4)---- specifications for TachoSil IP (-(b)(4)-) and TachoSil at release (-(b)(4)-) and comment on the consistency of these determinations.

22. Please specify the criteria for time of collagen sponge ---(b)(4)--- for Analytical Procedure 12242 (Test for identity - -----(b)(4)-----).

23. With respect to Raw Materials/Reagents, please:

- a. 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. Provide validation data for freedom of adventitious agents.
- c. Describe any incoming endotoxin and bioburden limit specifications and testing performed for components and materials on receipt.

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24. With respect to cleaning, please provide a justification for the use of -----(b)(4)----- as a cleaning agent for removal of potential prion contamination.
25. With respect to 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.
26. With respect to change in equipment used for -----(b)(4)----- of coating suspension: Page 10 of Section 3.2.P.2.3, Pharmaceutical Development of Manufacturing process, 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 because the former ---(b)(4)-- device is stated in the major process equipment list (section 3.2.A.1, page 14).

Administrative

27. You are seeking two indications for TachoSil in one BLA. At the Mid-Cycle stage of review, we have identified several concerns regarding the licensure of TachoSil for the -(b)(4)- indication (see comments above). We have requested additional information to help us address our concerns, particularly regarding the ----(b)(4)---- studies.

END

Please submit your responses by December 16, 2009 so that we can continue the review of your application.

If you have any questions, please contact the Regulatory Project Manager, Jie He, at (301) 827-9167.

Sincerely,

Jie He

Regulatory Project Manager
HFM-380, FDA/CBER
Office of Blood Research and Review
Division of Blood Applications
301-827-9167 fax 301-827-2857
email: jie.he@fda.hhs.gov

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Information provided by: N.Ananyeva; K. Lindsey; Date: 24-Nov-09

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Approved by N. Jain_____ Date 24-Nov-09 Transmitted by J. He_____ Date 25-Nov-09

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Thank you.

Number of pages (including cover sheet) 7