

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



Pharmacology / Toxicology Review

To: File (STN 125351/0- Original BLA Final Review)

From: La’Nissa A. Brown, Ph.D., Pharmacologist, Division of Hematology (DH)/OBRR

Through: Iftekhar Mahmood, Ph.D. Team Lead, Pharmacology/Toxicology Group, Hematology/OBRR

Subject: Filing of Final Pre-Clinical Review of STN 125351/0 – Nycomeed’s Original BLA for Fibrin Sealant Patch [TachoSil™]

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I. Background

Nycomed, Denmark, has created a equine-derived collagen fibrin sealant patch (proposed trade name TachoSil) containing thrombin and fibrinogen proposed for indication as an adjunct to hemostasis in surgery. TachoSil, or TachoComb S, is a modified third generation fibrin sealant adjunct is being processed for improvement of hemostasis and -----(b)(4)----- with local application to wounds surfaces following ineffective control of bleeding after conventional surgical techniques. TachoSil was derived for elimination of bovine aprotinin, a protease inhibitor to prevent transmissible bovine diseases to humans and theoretical possibility of immunogenic reactions. Predecessors of TachoSil have

been in use for several years in Europe and in the U.S. in over 400,000 patients including TachoComb H, Tachotop and TachoComb with similar indications for treatment.

II. Proposed Use and Doses

TachoSil will be administered as an adjunct postoperative as prescribed by clinician in three sizes: mini, standard and midi at approximately 2 standard pads per surgery. The approved indication is 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.

III. General Comments

- The non-clinical studies demonstrate TachoSil™ is safe and effective
- General safety concerns will continue to be monitored during on-going clinical studies including immunogenicity concerns, re-bleeding at target sites, maximal dose determination & validation
- TachoSil™ promotes the healing process immediately a target site
- TachoSil™ complete degradation & resorption is not clearly defined; but appears to be between -(b)(4)- months based on non-clinical studies.
- TachoSil™ appear to be well tolerated and poses no greater risks than similar products

IV. Recommendations

Recommendation on BLA:

Based on the review of pharmacological and toxicological data presented, I recommend the filing of this Biologics Licensure Application (BLA) STN 125351/0 for Fibrin Sealant Patch [TachoSil™]

Recommendation for non-clinical studies:

Nycomeed has completed an extensive non-clinical program to demonstrate the safety and effectiveness of TachoSil™ in the pharmacology and toxicology data presented sufficiently to support human use. Based on these findings in addition to its long-standing history in clinical applications, TachoSil™ poses no greater safety concerns of risks than similar products currently marketed. To note, please monitor for adverse events including immunogenicity concerns, thromboembolic episodes, and re-bleeding at target site as expected with similar biologic products. The overall safety profile of TachoSil™ has been adequately established for clinical applications.

I have no request for any further non-clinical evaluation at this time. There is no outstanding issue that preventing this BLA according to FDA guidelines from a pre-clinical standpoint.

V. List of Non-clinical Studies in BLA 125351/0

- **Study Report 185-2008** – A Comparison between TachoComb and TachoSil for Surgical hemostasis in Cardiovascular Surgery: An animal Experimental Study
- **Study Report 5205** – Ex Vivo Evaluation of Fleece-bound Tissue Sealing: Prepare –to-use vs. Ready –to-Use Technique with Special Emphasis on Apotinin
- **Study Report 5096** – Equine Collagen Sheet Coated with Human Fibrinogen and Human Thrombin- Equine Collagen Sheet Uncoated as Reference
- **Study Report 5130-1** -----(b)(4)----- Application of TachoComb and TachoComb S: ----(b)(4)---- Reaction and Hemostatic Effectiveness
- **Study Report Number 5084-1** – Efficacy of TachoSil Haemostatic Wound Healing in -(b)(4)-
- **Study Report 5107-1** - Comparative hemostatic Wound Sealing Effect and Resistance of Absorbable TachoComb H and TachoComb S _Experimental Study Design in the Pig Model of -----(b)(4)-----
- **Study Report Number UL/5054** - Optimal Tensile and Adhesive Strength of TachoComb and TachoComb H in Rats
- **Study Report 5055** - Study of the Adhesion Conditions of TO-193 (TachoComb)
- **Study Report Number UL/5057** – Adhesive Efficacy of TachoComb in Rats, Guinea pigs, -(b)(4)-
- **Study Report Number UL/5056** – Optimal Tensile and Adhesive Strength of TachoSil in Rats, Rabbits and *In Vitro* model
- **Study Report Number 5083-1** - Efficacy of TachoComb and TachoComb H Haemostatic Wound Healing in -(b)(4)-
- **Study Report Number 103/37** – Neurotoxicity of TachoComb in Rats, Guinea Pigs, and Dogs
- **Study Report Number UL/5060** - Pharmacokinetics of TachoSil, its predecessors and Tachotop in Rats
- **Study Report Number UL/5095** - Metabolism of TachoComb in -(b)(4)-
- **Study Report UL/5080 (#94/245)** - Intraperitoneal Toxicity Study with Single Insertion in Dogs (TachoComb-Human Thromobin)
- **Study Report Number UL/5085-** Intraperitoneal Toxicity Study with Single Insertion of TachoComb-Human Thromobin in -----(b)(4)----- Rats

- **Study Report 5095-1** Safety Study with Sequential Evaluation of Degradation and Local Tolerance after Single Intraperitoneal Application in Dogs
- **Study Report 103-2-1-** The Effectiveness of a Fibrinogen-Thrombin-Collagen Based Hemostatic Agent in an Experimental -----(b)(4)-----
- **Study Report 103-5-1** – Application of Fibrinogen-Thrombin-Collagen Based Hemostatic Agent in an Experimental -----(b)(4)-----
- **Study Report 103-74** Periodical Observation of TO-193 (TachoComb) Applied onto Liver in Rats
- **Study Report N00001569** – Four week Repeat Dose Toxicity of TachoSil in Minipigs
- **Study Report r-bp 1270-1** 4 week Repeat Dose Toxicity of Tachosil in ---(b)(4)-- Minipigs
- **Study Report 103-29-1** Toxicity Study of Tachocomb (TO-193) in rats and dogs single intraperitoneal administration.
- **Study Report Number UL/5059** – Study of Pharmacokinetics of TachoComb by Means of Intraperitoneal Application in Rats (Liver Adhesion)
- **Study Report Number 103/74** - Periodical Observation of TO-193 (TachoComb0 Applied to the Liver in Rats
- **Study Report Number SR306/2008** - Metabolism of TachoSil, TachoComb and Tachotop in Guinea Pigs
- **Study Report Number UL/5095** Safety Study with Sequential Evaluation of Degradation and Local Tolerance after Single Intraperitoneal Application in Dogs
- **Study Report Number 103/2** – Metabolism of TachoComb in -(b)(4)-
- **Study Report Number 103/5** – Metabolism of TachoComb in -(b)(4)-
- **Study Report Number 103/29** – Toxicity Study of Tachocomb in Rats and Dogs Single Intraperitoneal Administration
- **Study Report Number UL/5150-** Acute Toxicity of Tachotop in Rats
- **Study Report Number UL/4829** – Testing of TachoTop for Immunological Tolerance in Repeated Local Implantations in Guinea Pig
- **Study Report Number UL/4830-** Cell Mediated Immune Reaction of the Skin Sensitized Guinea Pigs for Testing of Possible Antigenic Properties of TachoTop Flocculi

- **Study Report Number 103/28-** Antigenicity Studies following Intraperitoneal Administration of TachoComb in Guinea Pigs
- **Study Report Number UL/4829 and UL 4830** – Antigenic Study in Guinea Pigs Following Subcutaneous Administration of Tachotop
- **Study Report Number UL/5161** – Investigation into the Presence of Neoepitopes in 5 Gamma Irradiated Proteins (Antigenicity Studies Following Subcutaneous Administration of Tacho Components in Rats)
- **Study Report Number 103/27** – Four-Week Repeat Dose Toxicity Studies Following Intraperitoneal Administration of TachoComb in Rats
- **Study Report BP 1279** - Two week Toxicity of TachoSil (maximum tolerated single dose) in ---(b)(4)--- Minipigs
- **Study Report BP 1270** – Four Week Repeated Toxicity of TachoSil in ---(b)(4)--- Minipigs
- **Study Report 28-2008-1 and 2** – Toxicity of TachoTop, TachoComb H and TachoSil in ----(b)(4)---- Minipigs for hemostasis in Liver and Spleen Surgery for 1 Week, 4 Weeks, and 13 weeks after Single Application

VI. Summary of Relevant Non-clinical Studies in BLA 125351

Study Report Number UL/5059 – Study of Pharmacokinetics of TachoComb by Means of Intraperitoneal Application in Rats (Liver Adhesion)

Study Report Number 103/74 Periodical Observation of TO-193 (TachoComb0) Applied to the Liver in Rats

These two studies were the same, just under different numbers.

The purpose of the study is to determine the pharmacokinetics of TachoComb fleece with various doses of Thrombin and Fibrinogen (FIB) vs. sham in i.p. administration on liver adhesion in the -(b)(4)- rat model.

Patch Size/Animal	Patch Dose	Thrombin	FIB	WK 2	WK 4	WK 8	WK 12	WK 16	WK 20
Control (sham)	0	0	0	3	3	3	3	3	0
0.25 cm ²	11.0 mg/kg	2 IU/kg	5.5 mg/kg	5	5	5	5	0	5
1.00 cm ²	43.9 mg/kg	8 IU/kg	22 mg/kg	0	5	5	5	5	0
2.25 cm ²	98.7 mg/kg	20 IU/kg	55 mg/kg	0	0	5	5	5	0

Animals (n~3-5/gr.) were dosed acutely at liver wound (laparotomy) and followed for 2,

Dose groups:	Drug product	Patch size / animal	Patch dose	Thrombin	Fibrinogen
	TachoSil	45.6 cm ²	48.5 mg/kg	6.04 IU/kg	15.1 mg/kg

4, 8, 12, 16 & 20 weeks. Clinical observations were monitored (BW, behavior, etc.). There were no overt toxicities at the end of the study and the product still had remnants at the 20 week timepoint. It appears degradation is directly proportional to the size /dose of the pad and wound size.

Comment: There are concerns with complete degradation of TachoSil that have already been conveyed to the Sponsor and will be addressed in BLA 125351 submission. Study design was not consistent in the N selection at each relevant timepoint or size/dose of pad.

Study Report Number 28-2008-1 Toxicity of TachoComb (TO-193) in rats and dogs single intraperitoneal Application to Rats (Liver Adhesion)

The aim of this study is to evaluate the acute dose toxicity of TachoComb products following long term observation (4 wks.) using the minipig animal model. In PK study, minipigs (n=3/gr) were acutely dosed as follows:

Group	Mean cumulative Dose [mg/kg/minipig]	Administered number of fleece per minipig	Number of minipigs [F] per duration of treatment		
			7 days	28 days	92 days
1 (Control)	0	-	3	3	3
2 (Tachotop)	6.4	1	3	3	3
3 (TachoComb H)	47.2	1	3	3	3
4 (TachoSil)	48.5	1	3	3	3

The NOEL was determined to be the largest size tested (single std. pad). At Day 93, TachoSil and TCH are not biodegraded (remnants of fleece are still detectable) as evident by granulation, increase neutrophils, etc. The healing process is promoted through use of the products.

Animals were followed up to 13 weeks after laparotomy and wound creation in liver and spleen. Time to hemostasis (TTH) was up to 4 mins and negative control was manual pressure. Fleece was standard (9x5 cm) size. Clinical observations were noted (behavior, BW, HR, mortality, etc.), and complete serum/clinical chemistry panel, urinalysis, histopathology were observed. There were no signs of overt toxicity in clinical observations or parameters monitored including complete serum chemistry panel, histopathology. There was hematoma formation, hemorrhage, and fibrin clot formation

within the first week in all Tacho product treated groups. By Day 93, TachoComb H (TCH) and TachoSil (TS) showed fibrin clot formation and granulation tissue and remnants of fleece (although the collagen fleece is claimed to be completely resolved). It appears that TachoSil slowly degrades but does not cause overt toxicity by Day 93.

Comment: It appears that TachoSil will be as well tolerated as its predecessors. However, the complete resorption of the final product has yet to be determined. It will be necessary to monitor this safety concern in clinical setting.

Study Report Number 5127-1 Comparative Hemostatic Wound Sealing Effect and Resistance of Absorbable TachoComb H and TachoComb S- Experimental Study in the Pig in a Model of -----(b)(4)-----

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

Study Report Number 5084-1 Comparison of the Efficacy of TachoComb H and TachoComb S in -----(b)(4)----- in the Dog

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

Study Report r-bp 1270-1 4 week Repeat Dose Toxicity of Tachosil in ----(b)(4)--- Minipigs

The aim of this study is to address the toxicity and PK of TachoSil of latest formulation to correlate/ bridge predecessor data in minipig model. Animals (n=6) were dosed Tachosil or control buffer (n=3, non-coated collagen patch) via i.p. (laparotomy to spleen

and liver) administration in wound (2-3 cm²) with 5 mins. pressure on Days 1, 2 and 22 followed by necropsy (Day 7 and 28).

Patch size/animal	Patch dose	Thrombin	Fibrinogen
138.8 cm ²	79.1 mg/kg	9.9 IU/kg	27.1 mg/kg

Total dose ~732 mg

Comment: There was only one dose selected and the absence of a negative control may skew results.

Study UL/5060 – Pharmacokinetics of ¹²⁵I-TO-193 – Tissue Distribution and Excretion after Single Application

The aim of this study is to follow the distribution and absorption of TachoComb in Rat to support the safety and efficacy of the product profile. The highest level of distribution was noted at 6 hours after administration and highest dose of product remained at target site of treatment. Degradation begins quickly and degraded product is rapidly distributed without accumulation. The product is distributed throughout the body in moderation compared to target site.

Comments: This study was completed in April 1994 and was not with the latest version of the product so it does not accurately reflect the distribution and excretion of product, but can be used to estimate results for final product.

Study Report Number UL/5095 Safety Study with Sequential Evaluation of Degradation and Local Tolerance after Single Intraperitoneal Application in Dogs

The aim of this study is to evaluate the long-term effect of TachoComb following 32 mg/kg administration in Dogs. Animals were followed 2, 4, 6, 12, and 24 weeks (6 months). It was determined that only remnants of the pad were still detected at end of study ~5% of patch. It appears that the degradation of the pad is dependent on the size of the wound= larger wound/patch→faster degradation. Due to recruitment of neutrophils & eosinophils and fibronolysis increased to improve the healing process.

Comment: Results indicate clinical monitoring of complete degradation is necessary in clinical trials.

Study Report 185-2008 – A Comparison between TachoComb and TachoSil for Surgical hemostasis in Cardiovascular Surgery: An animal Experimental Study

The aim of this study is to investigate the efficacy of TachoSil vs. TachoComb in a cardiovascular model (thoracotomy, sternotomy). Female guinea pigs were treated at aorta and right atrium (3 mm) topically with TachoSil or TachoComb in heparinized and non-heparinized to mimic clinical setting. TTH in heparin treated animals ~34mins vs. 1-14 mins. in non-heparinized animals with no differences in Tacho products. Cardiovascular parameters indicated no differences in treatment groups. The results indicate that the Tacho products are well tolerated and effective for intended indication. There were no overt toxicities or significant changes to clinical signs monitored in this study.

Study BP – 1270 Four Week Repeated Toxicity of TachoSil in ----(b)(4)---- Minipigs

The aim of this study is to determine the repeat dose toxicity of TachoSil in minipigs at higher doses to correlate to worst case clinical scenarios in TachoSil application. Minipigs were dosed 79.1 mg/kg in hepatic resection model on Day 1, then dose on Day 22, in same animal on spleen lesion model. Necropsy was performed on Day 29 and Day 50. There were no notable findings in clinical signs or parameters monitored. It appears that TachoSil in repeat use in moderation would not pose any greater risk than single use of the product.

Comment: It appears TachoSil is tolerable over time course of this study; however, the patch was not completely resorbed on Day 50. Clinical monitoring will be completed to determine final degradation.

Study Report 103/27 – Four Weeks Repeat Toxicity Study of TachoComb (TO-193) by Intraperitoneal Administration to Rats

The aim of this study is to examine the toxic effects of multiple application (in situ) of TachoComb in rats to mimic clinical setting. Rats (n=10 gr. and 5 recovery/gr. M/F) were dosed once weekly by applying pad into abdominal cavity by laparotomy (intraperitoneal) and monitored for 4 weeks (sacrificed 1 or 4 weeks post dose). The highest dose tested was 1044 mg/kg and there were only mild changes in clinical signs at dose (decrease in BW, water intake by animals, decrease in neutrophils and slight increase in lymphocytes but signs were reversible). There were no overt toxicities noted in this study. There were signs of adhesion in all groups as expected (dose dependent indicated by accumulation of neutrophils and granulated tissue). The NOAEL was determined to be 31 mg/kg and product was well tolerated in repeat administration.

Comment: This study does not adequately address multiple single use dosing concerns as animals are staggered in dosing regimen (once weekly) as opposed to repeatedly or singly dosed with multiple pads to examine the potentiating effect of product.

Study Report BP 1279 – Two-week Toxicity of TachoSil (maximum tolerated single dose) in ----(b)(4)---- Minipigs

The aim of this study is to determine the maximal tolerated dose for TachoSil in minipigs followed by a 2 week observation (recovery period). Mini pigs were dosed 444 or 580 mg/kg (10-15 standard size patches). Clinical observations were completed including complete serum chemistry panel. It appears that both doses were tolerable and the NOAEL is ~15 patches for 2 weeks. Within days, granulation formation occurred, neutrophils and eosinophils presented within hours. It appears that the collagen pad acts as a scaffold to initiate and promote the healing process that begins rapidly after administration.

Comment: The long term effects were not examined (> 2 wks). The maximal dose tested in clinical trials (TC 016) was 7 pads at 73 mg/kg in hepatic resection model.

Study Report Number 103/28- Antigenicity Studies following Intraperitoneal Administration of TachoComb in Guinea Pigs

The aim of this study is to evaluate the antigenicity of TachoComb in guinea pigs. This was a single dose test in lesion model. There were no signs of antigenicity in animals tested. TachoComb appears to be tolerable in animals tested.

Study Report Number UL/4829 and UL 4830 – Antigenic Study in Guinea Pigs Following Subcutaneous Administration of Tachotop

The aim of this study is to investigate the antigenicity of Tacho products in guinea pigs based on antibody development. Specifically, the biological components of equine collagen, thrombin (human and bovine) and fibrinogen, were tested for their ability to induce antigenic responses based on -----(b)(4)-----.

The results demonstrated that Tacho products will likely be well tolerated and not produce antigenic responses related to use of the product.

Comment: This study is at best supportive data. The study is designed based on theoretical assumptions and cannot be validated or correlated to clinical response. Data is tool in supporting the safety profile of this product.

Study Report Number UL/5161 – Investigation into the Presence of Neopeptides in 5 Gamma Irradiated Proteins (Antigenicity Studies Following Subcutaneous Administration of Tacho Components in Rats)

The aim of this study is to predict the antigenicity of Tacho products based on hypersensitivity and local responses in rats. There were no significant findings in this study although findings are at most theoretical. Tacho products do not appear antigenic. Results were similar in all animal models tested.

Study Report Number UL/5095 Safety Study with Sequential Evaluation of Degradation and Local Tolerance after Single Intraperitoneal Application in Dogs

The aim of this study is to evaluate the degradation, PK and tolerance of TachoSil and its components singly in a liver lesion (pressure 4 mins.) at 2, 4, 6, 12 and 24 weeks in a -(b)(4)- dog model. Products were delivered intraperitoneal (laparotomy: 8.1-12.2cm²) to dogs (n=3 M/gr., T=15 animals). There were no overt toxicities noted or significant changes in clinical signs monitored including complete serum chemistry panel and clinical observations. Healing from surgery was similar in all test articles with no significant differences in signs of local irritation, coloration or histopathology of targeted site. It appears that TachoSil will be well tolerated compared to currently marketed products and methods of treatment.

Patch size/animal	Patch dose	Thrombin	Fibrinogen
24 cm2	32 mg/kg	4 IU/kg	10 mg/kg

Comment: This study was completed in 1997 and not on the final new product (predecessor tested).

General Comments: The remaining pre-clinical g studies demonstrated the safety and effectiveness of Tacho products (predecessors) in efficacy models, bridging comparative

studies on Tacho products, and studies to determine the degradation/metabolism of Tacho products. Studies' findings indicate that TachoSil is well tolerated, effective, and adequate safety profile for clinical use.

VII. Summary Basis for Regulatory Action for Non-Clinical Review in Executive Summary

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 investigate safety 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.

TachoSil was tested up to 5 times and 7.5 times the intended clinical dose (~2 standard size pads/surgery) up to two weeks without any adverse events in the pre-clinical program. 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 until complete 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)-----
----- similarity) for alpha-1 and alpha-2 chains, respectively. High homology between human and equine proteins and high abundance of collagen -(b)(4)-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)- using -----(b)(4)----- on days 1, 11, 29, 40, 59, 73, 85 and 106, and were found comparable for both types of antisera.

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. The safety profile determined for TachoSil is satisfactory to allay the immunogenicity concern to the extent which studies in animals can support (see Guidance ICH M3 for Pharmacological/Toxicological studies). Further evaluation of immunogenicity of TachoSil will be performed in clinical studies conducted by Nycomed under an Investigational New Drug application (IND) -----(b)(4)----- . 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 demonstrate the safety and effectiveness of TachoSil. Based on these findings in addition to its clinical history, TachoSil poses no greater safety concerns of risks than similar products currently marketed. The Pharmacology/Toxicology Reviewer recommends approval of this BLA.