Summary Basis for Regulatory Action

Date: July 20, 2015

From: Charles Maplethorpe M.D., Ph.D. CBER/OBRR/DHCR/HPRB

BLA/ STN#: 125351/172

Applicant Name: Takeda Pharma A/S

Date of Submission: June 20, 2014

PDUFA Goal Date: April 20, 2015 extended to July 20, 2015

Proprietary Name/ Established Name: TachoSil

Indication: TachoSil is a fibrin sealant patch indicated for use with manual compression in adult and pediatric subjects as an adjunct to hemostasis in cardiovascular and hepatic surgery, when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Paul D. Mintz, MD, Director
Division of Hematology Clinical Review, Office of Blood Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review Charles Maplethorpe	STN125351/172; SBRA of STN125351/0
Clinical Pharmacology Review	N/A
Statistical Review	Chunrong Cheng, Ph.D.
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	Bioresearch monitoring inspections were not conducted for this BLA
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A

1. Introduction

STN125351/172 is an efficacy supplement submitted by Takeda Pharma A/S to add the adjunct to hemostasis in hepatic surgery indication to TachoSil. This efficacy supplement also fulfills Post-Marketing Requirement (PMR) #1 in the April 5, 2010, approval letter for TachoSil, which required a pediatric hepatic resection surgery study to satisfy the Pediatric Research Equity Act (PREA) requirements.

The results of study TC-4202-040-SP demonstrate the safety and efficacy of the use of TachoSil as an adjunct to hemostasis in hepatic surgery in adults and pediatric subjects. The safety profiles of the adult hepatic resection study in this submission, and the adult cardiovascular study used for product licensure are similar. Although the pediatric hepatic resection study was small, the safety profile was similar to that of the adult hepatic resection study. Consequently, through extrapolation, we consider pediatric use of TachoSil as an adjunct to hemostasis in cardiovascular surgery, the approved indication, to be as safe as its use in hepatic surgery.

2. Background

Fibrin Sealant products are an external source of thrombin and fibrinogen, the components required to form a clot. TachoSil is an equine collagen patch coated with human thrombin and human fibrinogen. TachoSil was licensed on April 2, 2010, as an adjunct to hemostasis in cardiovascular surgery in adults when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. Following discussions with the Pediatric Research Committee (PeRC) on March 10 and March 31, 2010, CBER agreed with the applicant's proposal to use data from a pediatric study in hepatic surgery to satisfy the PREA requirements for all surgical settings for the adjunct to surgical hemostasis indication.

3. Chemistry Manufacturing and Controls (CMC)

See the SBRA for STN125351/0 for a discussion of CMC issues for TachoSil.

4. Nonclinical Pharmacology/Toxicology

See the SBRA for STN125351/0 for a discussion of nonclinical studies of TachoSil.

5. Clinical Pharmacology

Not applicable.

6. Clinical/Statistical

a) Clinical Program

Clinical study TC-2402-040SP was a randomized, open label, active-controlled, multicenter study comparing TachoSil (test) to Surgicel (control) as an adjunct to surgical hemostasis in adults and pediatric subjects undergoing hepatic resection surgery. The primary endpoint was the proportion of subjects achieving hemostasis at a pre-identified bleeding site within 3 minutes of study agent application. Secondary endpoints were the proportion of subjects achieving hemostasis at the pre-identified bleeding site within 5 or 10 minutes.

There were 244 adult subjects randomized (114 TachoSil, 110 Surgicel), and are referred to as the Full Analysis Set (FAS). Safety was evaluated in the exposed subjects (114 TachoSil, 109 Surgicel; one subject randomized to Surgicel did not receive the study agent), and are referred to as the Safety Analysis Set (SAF). The pediatric study randomized subjects 1:1 to TachoSil or Surgicel, until a total of 20 subjects were treated with TachoSil, or until the adult enrollment (244 subjects) was completed, at which point all pediatric subjects would be treated with TachoSil for a total of 20 TachoSil pediatric subjects.

In the adult study, a similar proportion of male subjects and female subjects were randomly assigned in the trial (53% and 47%, respectively). The mean (SD) age of subjects was 58.1 (13.95) years, and in both treatment groups approximately 30% of the subjects were above 65 years. The majority of subjects were White/Caucasian (80%), and the most common ethnicity was non-Hispanic/non-Latino (88%).

In the pediatric study, a similar proportion of male and female pediatric subjects were treated overall (48% and 52%, respectively). The majority of subjects were White/Caucasian (79%) and the most common ethnicity was non-Hispanic/non-Latino (69%). The mean age was slightly higher in the TachoSil group (4.58 years; range 0.4, 13.0 years) than in the comparator group (3.77 years; range 0.4, 16.0 years).

Study TC-2402-040-SP demonstrated efficacy for both adult and pediatric groups, as shown in Tables 1 and 2:

Table 1: Logistic Regression Models of Proportion of Adult Subjects with Hemostasis within 3 Minutes

Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison TachoSil - Surgicel Original		
			Odds Ratio (SE)	Wald 95% CI	*P* value
FAS					
TachoSil	92/114 (80.7)	(72.3, 87.5)			
Surgicel Original	55/110 (50.0)	(40.3, 59.7)	4.87 (1.60)	(2.55, 9.29)	<0.001
PP					
TachoSil	81/99 (81.8)	(72.8, 88.9)			
Surgicel Original	52/99 (52.5)	(42.2, 62.7)	4.83 (1.75)	(2.37, 9.82)	<0.001
Sensitivity Analysis[1] (FAS)					
TachoSil	92/114 (80.7)	(72.3, 87.5)			
Surgicel Original	56/110 (50.9)	(41.2, 60.6)	4.73 (1.56)	(2.47, 9.03)	<0.001

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set – subjects compliant with the protocol; SE, standard error.

Percentages are based on the number of subjects with time to hemostasis in the FAS.

The proportion of subjects with hemostasis within 3 minutes was analyzed by using a logistic regression model with treatment and pooled center as factors.

[1] Missing values in the Surgicel Original group were counted as having hemostasis within 3 minutes and those in TachoSil group were counted as not having hemostasis within 3 minutes.

P values are 2-sided.

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Table 2: Difference in Proportion of Pediatric Subjects with Hemostasis within 3 Minutes

Treatment	%	Exact Binomial CI	Pairwise Comparison TachoSil - Surgical Original	
			(%)	Exact Binomial
Pediatric FAS				
TachoSil (n=8)	87.5	(47.3, 99.7)	43.1	(-4.9, 85.5)
Surgicel Original (n=9)	44.4	(13.7, 78.8)		
Pediatric SAF				
TachoSil (n=20)	85.0	(62.1, 96.8)	40.6	(0.4, 80.8)
Surgicel Original (n=9)	44.4	(13.7, 78.8)		
Pediatric EXT				
TachoSil (n=12)	83.3	(51.6, 97.9)	–	–

CI, confidence interval; EXT, extension set, FAS, full analysis set; SAF, safety analysis set.
Percentages are based on the number of subjects with time to hemostasis in the relevant population.
The proportion of subjects with hemostasis within 3 minutes (n) was analyzed by using an exact binomial method.
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In both the adult and pediatric studies, the use of TachoSil resulted in more rapid hemostasis. This is shown by the higher proportion of subjects who achieved hemostasis at the target bleed site within 3 minutes, as compared with the control group. In the adult study, 80 percent of subjects who received TachoSil achieved hemostasis within 3 minutes, as compared with only 50 percent of the control group. Further, the control group's result of 50 percent was excluded by the lower bound of the 95 percent confidence interval. In the pediatric study, a similar result was observed; however the small sample size limited the statistical analysis.

b) Pediatrics

The Pediatric Study Plan (PSP) was presented to the PeRC, and discussed with them on March 10 and March 31, 2010, in conjunction with the initial approval of TachoSil for the adjunct to surgical hemostasis in cardiovascular surgery indication. PeRC recommended that pediatric studies in cardiovascular surgery be conducted; however, the applicant stated that such studies would be problematic because of a low enrollment, and the heterogeneous nature of bleed sites that would be studied. The applicant proposed that the PREA

requirement be satisfied by enrolling pediatric subjects into the planned liver surgery study TC-2402-040-SP. CBER/OBRR agreed with this proposal.

When study TC-2402-040-SP was completed after enrolling 20 subjects into the TachoSil arm, there were no subjects in the neonate (0 to 28 days of age) category; therefore, the pediatric indication excludes neonates.

c) Other Special Populations

Not applicable.

d) Overall Comparability Assessment

TachoSil has been studied as an adjunct to surgical hemostasis in cardiovascular and liver surgery in adults and pediatric subjects (excluding neonates), and similar safety and efficacy has been observed across studies.

7. Safety

In study TC-2402-040-SP, there were 114 adult subjects exposed to TachoSil; 16 of these 114 subjects received a second application of TachoSil. In the pediatric component of study TC-2402-040-SP, there were 20 pediatric subjects exposed to TachoSil; one pediatric subject received a second application of TachoSil.

There were 1051 adverse events (AE) reported in the 107 TachoSil-exposed adults; 85 of these AEs were categorized as serious, and occurred in 44 adults. AE rates were similar in the TachoSil and control arms, and appeared to be related to the underlying medical condition. The most frequently reported adverse reactions were nausea (30% of subjects) and anemia (23% of subjects). Post-operative bile leakage was observed in 8 (7%) of subjects after treatment with TachoSil and 13 (12%) after treatment with comparator.

In the pediatric component of study TC-2402-040-SP, there were 156 AEs reported in the 20 TachoSil-exposed pediatric subjects; 34 of these AEs were categorized a serious, and occurred in 12 pediatric subjects. AE rates were similar in the TachoSil and control arms, although the small sample size of the pediatric cohorts does not allow a reliable estimation of event rates. The AEs appeared to be related to the underlying medical conditions.

There were 4 deaths in the TachoSil adult study arm, and 1 death in the TachoSil pediatric study arm. The adult deaths were from cardiorespiratory, gastrointestinal hemorrhage, multi-organ failure, and hepatic failure. The pediatric death was in a 6 month old female who experienced disseminated intravascular coagulopathy with exsanguination after septicemia. All deaths appear to be related to the underlying medical conditions.

Immunogenicity

TachoSil is comprised of two active substances – human fibrinogen and human thrombin – coated onto an equine collagen sponge. Study TC-2402-040-SP monitored the adult subjects for antibody formation to 1) equine collagen and 2) human fibrinogen. In the TachoSil arm, 27 of the 96 adult subjects assessed were found to have developed equine collagen antibodies, 25 (26%) of whom were considered truly immunized. One adult in the TachoSil group developed fibrinogen antibodies.

During the long-term safety follow-up, 7 of 14 (50%) available subjects were still positive for equine antibodies approximately 1.5 to 2 years after exposure. However, no cross-reactivity between equine collagen antibodies and human collagen was identified, and no new medical conditions that could have been potentially related to the development of antibodies were reported.

The single adult subject developing antibodies against fibrinogen still had antibody titers at long-term follow-up; however, no coagulation abnormalities or medical conditions potentially related to fibrinogen antibodies have been noted.

Although the antibodies to the equine collagen component of TachoSil were found to be common in this clinical study, they appear to have minimal to no clinical impact. The results of the extension trial confirm the conclusions of the main trial, and the benefit-to-risk ratio of TachoSil remains favorable.

8. Advisory Committee Meeting

STN125351/172 was not presented to the Blood Products Advisory Committee because there were no issues needed for them to address.

9. Other Relevant Regulatory Issues

With submission of the results from study TC-2402-040-SP, the applicant has satisfied the PREA requirements for all adjunct to surgical hemostasis indications. Therefore, the pediatric indication will be granted when additional adult adjunct to surgical hemostasis indications are added.

10. Labeling

There were no disagreements with the applicant over changes to the submitted labeling recommended by FDA.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The clinical reviewer recommended approval of STN125351/172.

b) Risk/ Benefit Assessment

The risk associated with the use of TachoSil as an adjunct to surgical hemostasis in adult and pediatric subjects is small and is out-weighed by the hemostatic benefit.

c) Recommendation for Postmarketing Risk Management Activities

Routine post-marketing surveillance is recommended.

d) Recommendation for Postmarketing Activities

There are no recommended post-marketing requirements or commitments for clinical purposes.