Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Through:	Meghna Alimchandani, MD Associate Director for Medical Policy, OBE, CBER
From:	Faith Barash, MD, MPH Medical Officer, Pharmacovigilance Branch Office of Biostatistics and Epidemiology (OBE) Center for Biologics Evaluation and Research (CBER)
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Takeda Pharma A/S
Product:	TACHOSIL (Fibrin Sealant Patch)
STN:	125351/279
Indication:	TACHOSIL is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients 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.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2019

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of an efficacy supplement (STN125351/172) for TACHOSIL on July 15, 2015, to expand the indication to include use in children.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

TACHOSIL is a fibrin sealant patch *"for use with manual compression in adult and pediatric patients 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*. Under the Limitations of Use, the package insert notes that Tachosil is "*not for use in children under one month of age*."

TACHOSIL is a collagen sponge of equine origin, coated with human fibrinogen and human thrombin. When in contact with a bleeding surface, the collagen sponge dissolves, and the thrombin-fibrinogen reaction initiates the coagulation cascade. All components of the product, including the collagen sponge, are expected to degrade in about 4-6 months. This product is manufactured by Takeda Austria GmbH, and distributed by Baxter Healthcare Corporation.

1.3 Regulatory History

- June 8, 2004: TACHOSIL was approved in Europe; and has since been marketed in 65 countries outside the US.
- April 5, 2010: Initial approval for TACHOSIL in the U.S. for use as an adjunct to hemostasis, when control of bleeding by standard surgical techniques is ineffective or impractical.
- July 15, 2015: Approval of efficacy supplement (STN 125351/172) to expand indication to include use in children **(trigger for this PAC)**

- 2016: FDAAA Title IX, Section 921 posting[1] for the potential signal of serious risk of intestinal obstruction in patients undergoing abdominal and/or pelvic surgery. (Please see discussion of this serious risk in section 5.1 of memo.)

- July 29, 2016: Approval of labeling supplement (STN 125351/213) which revised the package insert to include information on intestinal obstruction and ileus and to clarify the proper use of the patch. (Please see section 3 of memo.)

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for the PAC review period 7/15/2015 to 3/31/2019
- Manufacturer's Submissions
    - TACHOSIL U.S. package insert; updated June 8, 2018
    - Letter regarding dose distribution data, received July 2, 2019
- Pharmacovigilance Plan, Version 2.0, dated February 26, 2016
- FDA Documents
    - TACHOSIL Approval Letter, dated August 5, 2015
    - Division of Epidemiology Pharmacovigilance Review Memorandum dated April 5, 2010
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

On July 29, 2016, FDA approved a labeling supplement (STN 125351/213) which included information to clarify the proper use of the patch to avoid potential issues with adhesions based on review of all safety data for the product:

- Addition of text to Method of Application, section 2.2: *It is important to note that failure to adequately clean adjacent tissues may cause adhesions [see Warnings and Precautions (5.4)].*
- Addition of text to Warnings and Precautions, Section 5.4 Adhesions: *To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before administration of TachoSil [see Dosage and Administration (2.2)]. Events of adhesions to gastrointestinal tissues leading to gastrointestinal obstruction have been reported with use in abdominal surgery carried out in proximity to the bowel.*

[1] https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system-11

- Addition of text to Section 6.2 Postmarketing Experience: *Gastrointestinal disorders: intestinal obstruction (in abdominal surgeries), ileus (in abdominal surgeries).*

(Please see additional discussion of this serious risk in section 5.1 of memo.)

4 PRODUCT UTILIZATION DATA

Takeda provided the following patient exposure data for the period July 1, 2015 to March 31, 2019:

- U.S. postmarketing patient exposure was estimated as (b) (4) patients
- Worldwide postmarketing patient exposure was estimated as (b) (4) patients (includes (b) (4) patients in the European Union; (b) (4) patients in Japan; (b) (4) in other regions)

The sponsor based these patient estimates assuming an average use of one patch per procedure and per patient. Since the postmarketing exposure was based on sales/shipment data, it was not possible to further distinguish between pediatric and adult exposure.

These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN (PVP) AND POSTMARKETING STUDIES

5.1 Pharmacovigilance plan

The manufacturer's current Pharmacovigilance Plan for TACHOSIL is Version 2.0, dated February 26,2016.[2] Table 1 describes the important identified and potential risks, and missing information for TACHOSIL.

Table 1: TACHOSIL safety concerns and planned pharmacovigilance actions[3]

Identified Risks	**Planned Pharmacovigilance Actions**
Thrombotic and embolic events	Routine pharmacovigilance activities
Immunological events, including hypersensitivity	Routine pharmacovigilance activities
Gastrointestinal obstruction	Routine pharmacovigilance activities
Potential Risks	**Planned Pharmacovigilance Actions**
Transmission of infectious agents	Routine pharmacovigilance activities
Off-label use	Routine pharmacovigilance activities
Missing Information	**Planned Pharmacovigilance Actions**
Lack of experience on use in neurosurgery or in gastrointestinal anastomoses	Routine pharmacovigilance activities
Lack of experience in pregnant or lactating women	Routine pharmacovigilance activities
Lack of experience with repeated TACHOSIL use	Routine pharmacovigilance activities

[2] TACHOSIL® Pharmacovigilance Plan, Version 2.0

Gastrointestinal obstruction: Gastrointestinal obstruction is an identified risk, due to the adherent nature of the patch, as well as the nature of the surgeries requiring its use. This was added as an important identified risk in 2016, following the European medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) assessment and the sponsor's signal evaluation of gastrointestinal obstruction with TACHOSIL use. In November 2015, PRAC reviewed 6 cases of gastrointestinal obstruction; 4 of which had also been previously reported to FAERS. During the EMA evaluation of this safety signal, FDA concurrently conducted a comprehensive review of TACHOSIL spontaneous adverse event reports of gastrointestinal obstruction, additional EMA cases and literature case reports. There were 7 foreign reports in adults: 5 reports from FAERS (received 2012 – 2015) and 2 additional cases identified in the PRAC assessment. Three reports documented visual identification of bowel loop adherent to TACHOSIL; 1 report documented bowel adhesion to a "strange substance" (presumably TACHOSIL); 3 reports described intestinal obstruction in patients who had received TACHOSIL for a prior abdominal surgery but without visual confirmation of bowel adhesion. (See additional case details in section 6.)

In 2016, in accordance with FDAAA section 921, FDA publicly posted the potential signal of serious risk of intestinal obstruction in patients undergoing abdominal and/or pelvic surgery after TACHOSIL use, and the sponsor also distributed Direct Healthcare Professional Communication (DHPC) letters describing this risk. On July 29, 2016, FDA approved a label change to include additional information on this risk (please see details of label change in section 3 of the memo).

Thrombotic and embolic events: Fibrin sealants are blood clotting agents, designed to control hemostasis. As such, they carry a known risk of associated thrombotic and thromboembolic events.

Transmission of infectious agents: TACHOSIL is derived from human fibrinogen and human thrombin. As it contains plasma derived components, it carries a risk of transmission of infectious agents.

Other important identified and potential risks for TACHOSIL listed in the above table are common to the product class and are monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety studies or Risk Evaluation and Mitigation Strategy (REMS) for this product.

5.2 Postmarketing studies

The initial approval of TACHOSIL included a postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA): Study TC-2402-040-SP, "A randomized, open label, parallel-group, multi-center clinical trial to compare efficacy and safety of TACHOSIL versus Surgicel Original for the secondary treatment of local bleeding in adult and pediatric patients undergoing hepatic liver resection surgery."

Study status: The study was completed, and the final report submitted on February 28, 2014.[4] This study is the basis for the efficacy supplement that is the trigger for this PAC.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of TACHOSIL between 7/15/2015 (PAC trigger) and 3/31/2019. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event reports for TACHOSIL during the review period are listed in Table 2 below. There was one U.S. report and 47 foreign reports.

Table 2: FAERS Reports for TACHOSIL (7/15/2015 through 3/31/2019)

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious Foreign	Total, US	Total, Foreign
<18 years	0	2	0	0	0	0	0	2
≥18 years	0	22	0	2	0	0	0	24
Unknown	0	19	0	1	1	1	1	21
All ages	0	43	0	3	1	1	1	47

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions.

6.2.1 Deaths

There were 3 fatal reports, which were individually reviewed. There were no pediatric deaths. The death reports are summarized as follows:

[4] 014210/0.74 (Amendment)- Recd 02/28/2014- DATS#579188

- 50-year-old male with kidney tumor and “intense bleeding” post-operatively, developed bowel obstruction 7-10 days later and died of circulatory failure.
- 52-year-old female with acute pancreatitis and liver hemorrhage treated with TACHOSIL for control of hemorrhage, died from uncontrolled bleeding and hemorrhagic shock.
- Female of unknown age underwent laminectomy and was treated with both TACHOSIL and EVICEL to close the dura mater. She developed meningismus and abacterial meningitis.

6.2.2 Serious non-fatal reports

During the review period, there were 43 serious non-fatal reports, 2 of which involved pediatric patients (summarized below).

- 2-year-old male reported to have difficulty swallowing. Approximately 1 year previously, patient underwent surgery to correct an esophageal malformation. It was initially thought that there might be residual TACHOSIL, or that TACHOSIL had eroded into the esophagus. Upon surgical evaluation, it was discovered that the child had swallowed a piece of plastic, that had lodged in the area of the anastomosis.
- 4-year-old tested positive for HCV antibody. As the hepatitis C RNA was negative, it was considered a false positive result. The patient had rhabdomyosarcoma, blood products and transfusion. HCV-RNA PCR was below the lower limit of detection, and donor samples were negative for HCV-RNA PCR.

The most frequently reported MedDRA preferred terms (PTs) for serious non-fatal reports among all ages are summarized in Table 3. (Note that a report may have one or more PTs.)

Table 3: Top preferred terms (PTs) for serious non-fatal reports (7/15/2015 through 3/31/2019)

Preferred Term (PT)	Number of Reports	Label Status
Drug ineffective	7	PME
Off Label use	6	*Unlabeled*
Liver Abscess	4	*Unlabeled*
Anaphylactic Shock	3	WP, PME
Hepatitis C	3	WP, PME
Intestinal Obstruction	3	WP, PME
Product Adhesion Issue	3	WP, PME
Cerebrospinal fluid leakage	2	*Unlabeled*
Hepatitis C antibody positive	2	WP, PME
Meningitis Aseptic	2	*Unlabeled*

PME: Postmarketing experience; WP: Warnings and Precautions

Most reported MedDRA PTs are labeled events or consistent with an already labeled event. Other unlabeled PTs for are non-specific sporadic events or in association with post-operative complications. No other PTs appeared in more than 2 reports.

FAERS reports for gastrointestinal obstruction: There were 2 serious non-fatal reports for gastrointestinal obstruction in adults during the PAC review period, July 15, 2015 – March 31, 2019.

- 49-year-old female with ovarian cancer developed bowel obstruction on post-operative day 6. Ovarian cancer carries a known risk of intestinal obstruction.
- Female of unknown age developed intestinal obstruction after TACHOSIL used for hemostasis during Cesarean section.

Prior to the PAC review period (2012 – 2015), there were 5 additional serious non-fatal reports of gastrointestinal obstruction in adults:

- 72-year-old male, TACHOSIL used during surgery for bladder cancer, developed intestinal obstruction and perineal abscess.
- 54-year-old female, TACHOSIL used during surgery for large ovarian cyst, hysterectomy and bilateral adnexectomy. Patient had untreated Crohn's disease. Developed gastrointestinal obstruction on postoperative day 3. Patient underwent repeat surgery for lysis of adhesion and was discharged on postoperative day 7.
- 49-year-old female, TACHOSIL used during surgery for ovarian cancer. On postoperative day 6, patient developed gastrointestinal obstruction. Obstruction resolved with bowel rest and patient recovered.
- 50-year-old male, TACHOSIL used during surgery for kidney cancer with partial resection of the kidney. Patient was re-operated on for postoperative bleeding. Subsequently he developed bowel obstruction, later patient recovered.
- 81-year-old female, TACHOSIL, used during surgery for adenocarcinoma of colon. Hemicolectomy, hysterectomy and bilateral adnexectomy performed, patient developed bowel obstruction on postoperative day 1. Surgery for release of adhesions and bowel obstruction performed.

Reviewer comments: Malignancy carries a known risk of adhesion formation, due to metastatic lesions and complex surgical procedures.

6.2.3 Non-serious reports

During the reporting period, there were two non-serious reports (patients with age unknown), the reported PTs were hypersensitivity and anaphylactic reaction.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of TACHOSIL were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of May 17, 2019. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather,

they may serve as a signal for further investigation. A query of Empirica Signal using the Product (S) run identified the PTs summarized in Table 4, with a disproportional reporting alert. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 4: Data mining results

Preferred Term (PT) with EB05>2	**Number of Reports**	**Label Status**
Abdominal abscess	8	WP
Anaphylactic reaction	12	WP, C
Anaphylactic/anaphylactoid shock	12	WP, C
Biliary tract disorders	9	AR
Gastrointestinal Obstruction	12	WP, PME
Gastrointestinal perforation	13	PME
Gastrointestinal perforation, ulcer, hemorrhage, or obstruction	30	AR
Hepatic disorders	26	AR
Liver abscess	7	WP
Liver infection	16	WP
Lymphocoele	5	*Unlabeled*
Off label use	19	*Unlabeled*
Pancreatic fistula	4	*Unlabeled*
Post procedural bile leak	5	AR
Post procedural hemorrhage	6	AR
Product adhesion issue	8	WP
Product residue present	8	*Unlabeled*
Pseudomeningocele	3	*Unlabeled*
Pulmonary fistula	3	*Unlabeled*

PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

Most reported MedDRA PTs are labeled events or consistent with an already labeled event, and are reflective of use in abdominal surgery, particularly in complex liver surgery and cancer surgery. Other unlabeled PTs (lymphocele, pancreatic fistula, pseudomeningocele, pulmonary fistula) represent post-surgical complications and are confounded by indication during surgery. Product residue has been observed; all components of the fibrin sealant patch are expected to degrade by 4 – 6 months.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for TACHOSIL covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in FAERS. The periodic safety update report for period June 9, 2015 to June

8, 2016[5], classified gastrointestinal obstruction as a newly identified important risk. During the reporting period, in September 2015, following a request from the PRAC on July 10, 2015, the sponsor submitted an evaluation of the signal of intestinal obstruction, concluding that *"there is a causal relationship between application of TachoSil and GI adhesions leading to GI obstruction. However, there is no evidence that TachoSil use leads to an increase in the overall incidence of gastrointestinal adhesion/obstruction*." As a result, the sponsor updated the Summary of Products Characteristics (EU-SmPC), the Company Core Data Sheet (CCDS) and the EU-Risk Management Plan (RMP) to include gastrointestinal obstruction as an important identified risk. As noted previously, the sponsor also issued a Direct Healthcare Professional Communication (DHPC) letter, and FDA publicly posted this serious risk in accordance with FDAAA section 921. The sponsor revised the label to include additional information on this risk (previously discussed in sections 3 and 5.1 of memo.)

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database for peer-reviewed literature, with the search term "TACHOSIL" retrieved six articles. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety concerns for TACHOSIL were identified in these articles.

Article	Authors' Safety Conclusions
Use of Neoveil or TachoSi® to prevent pancreatic fistula following pancreaticoduodenectomy: A retrospective study. Kwon HE, Seo HI, Yun SP. Medicine. 2019 Apr;(17):e15293	Use of either TACHOSIL or Neoveil may reduce the incidence of postoperative pancreatic fistula.
Evolution of the surgical sealing patch TachoSil® in Peyronie's disease reconstructive surgery: Technique and comparative literature review. Hatzichriasrodoulou G. World J Urol. 2019 May 3.	TACHOSIL is a safe and effective graft in Peyronie's disease reconstructive surgery.
Sutureless repair for postinfarction left ventricular free wall rupture. Okamura H, Kimura N, Meno M. J Thorac Cardiovasc Surg. 2019 Feb 14.	Sutureless repair using TACHOSIL patch may be a viable treatment option for left ventricular free wall rupture.
Efficacy of a collagen-fibrin sealant patch (TachoSil®) as adjuvant treatment in the inguinofemoral lymphadenectomy for vulvar cancer: a double blind randomized controlled trial. Baggio S, Lagana AS, Garzon A. Arch Gynecol Obstet. 2019 May;299(5):1467-74.	Application of TACHOSIL does not seem to decrease postoperative lymphorrhea or complications.

[5] STN 125351/234

Article	Authors' Safety Conclusions
Results of TachoSil® associated with fibrin glue as dural sealant in a series of patients with spinal intradural tumors surgery. Technical not with a review of the literature. Mantano N, Pignotti F, Auricchio AM. J Clin Neurosci. 2019 Mar; 61:88-92.	Investigators' experience and literature review suggests that TACHOSIL after dural closure is safe and effective.
TachoSil® Dural Reconstruction in Extracranial-Intracranial Bypass Surgeries. Tews J, Jahromi BR, Ludtka C. J Neurol Surg Cent Eur Neurosurg. 2019 Jan;80(1):39-43.	Duraplasty with TACHOSIL enables elastic reconstruction of the dura perforation gap in standard extracranial-intracranial bypass surgeries.

8 CONCLUSION

This postmarketing pediatric safety review of adverse event reports, the sponsor's periodic safety reports, and the published literature for TACHOSIL does not indicate any new safety concerns. The PAC review was initiated due to approval for use in pediatric patients in 2015. There were no deaths reported in the pediatric age group (<18 years) during the review period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of TACHOSIL fibrin sealant patch.