<table>
<thead>
<tr>
<th>Application Type</th>
<th>Efficacy Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>STN</td>
<td>125351/172</td>
</tr>
<tr>
<td>CBER Received Date</td>
<td>June 20, 2014</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>April 20, 2015 extended to July 20, 2015 based on major amendment</td>
</tr>
<tr>
<td>Division / Office</td>
<td>DH/OBRR</td>
</tr>
<tr>
<td>Priority Review</td>
<td>No</td>
</tr>
<tr>
<td>Reviewer Name(s)</td>
<td>Charles M. Maplethorpe M.D., Ph.D.</td>
</tr>
<tr>
<td>Review Completion Date / Stamped Date</td>
<td></td>
</tr>
<tr>
<td>Supervisory Concurrence</td>
<td></td>
</tr>
</tbody>
</table>

**Applicant**
Takeda Pharma A/S

**Established Name**
Fibrin Sealant Patch

**(Proposed) Trade Name**
TachoSil

**Pharmacologic Class**
Human Thrombin and Human Fibrinogen on an Equine Collagen Patch

**Formulation(s), including Adjuvants, etc**
Patch applied topically to bleed site

**Dosage Form(s) and Route(s) of Administration**
Patch cut to size of bleed site, apply topically, repeat use permitted by labeling

**Dosing Regimen**

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

Limitations for TachoSil Use
Not for use in place of sutures or other forms of mechanical ligation in treatment of major arterial or venous bleeding.
| Orphan Designated (Yes/No) | No | Not for use in children under one month of age. |
STN125351/172
TachoSil (Fibrin Sealant Patch) (Takeda Pharma A/S)
as an adjunct to hemostasis for adult and pediatric hepatic resection surgery
Clinical Review Memo – Charles Maplethorpe, MD., Ph.D. CBER/OBRR/DHCR/HPRB

TABLE OF CONTENTS

GLOSSARY ...................................................................................................................................... 1

1. EXECUTIVE SUMMARY ............................................................................................................... 1

2. CLINICAL AND REGULATORY BACKGROUND ........................................................................ 1

   2.1 Disease or Health-Related Condition(s) Studied ................................................................. 1
   2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the
       Proposed Indication(s) ........................................................................................................ 1
   2.3 Safety and Efficacy of Pharmacologically Related Products .............................................. 1
   2.4 Previous Human Experience with the Product (Including Foreign Experience) ................. 1
   2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission ....... 1

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES ................................................. 2

   3.1 Submission Quality and Completeness .............................................................................. 2
   3.2 Compliance with Good Clinical Practices And Submission Integrity ................................. 2
   3.3 Financial Disclosures ........................................................................................................ 2

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES ...... 3

   4.1 Chemistry, Manufacturing, and Controls ......................................................................... 3
   4.2 Assay Validation ................................................................................................................ 3
   4.3 Nonclinical Pharmacology/Toxicology ............................................................................ 3
   4.4 Clinical Pharmacology ..................................................................................................... 3
       4.4.1 Mechanism of Action ................................................................................................. 4
       4.4.2 Human Pharmacodynamics (PD) .............................................................................. 4
       4.4.3 Human Pharmacokinetics (PK) ............................................................................. 4
   4.5 Statistical ........................................................................................................................... 4
   4.6 Pharmacovigilance .......................................................................................................... 4

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW ... 4

   5.1 Review Strategy ................................................................................................................ 4
   5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review .............................. 4
   5.3 Table of Studies/Clinical Trials ........................................................................................ 5
   5.4 Consultations .................................................................................................................... 13
       5.4.1 Advisory Committee Meeting (if applicable) ............................................................ 13
       5.4.2 External Consults/Collaborations ............................................................................ 13

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS .................................................. 13

   6.1 Trial #1 Study TC-2402-040-SP “A randomized, open label, parallel-group, multi-center
       trial to compare the efficacy and safety of TachoSil® versus Surgicel® Original for the
       secondary treatment of local bleeding in adult and pediatric patients undergoing hepatic
       resection surgery.” ............................................................................................................. 13
       6.1.1 Objectives (Primary, Secondary, etc) ....................................................................... 13
       6.1.2 Design Overview ..................................................................................................... 13
       6.1.3 Population ................................................................................................................ 14
       6.1.4 Study Treatments or Agents Mandated by the Protocol ............................................. 14
       6.1.5 Directions for Use ..................................................................................................... 15
       6.1.6 Sites and Centers ...................................................................................................... 15
       6.1.7 Surveillance/Monitoring ........................................................................................... 20
Reviewer Comment: The monitoring plan is standard for fibrin sealants for use as an adjunct to surgical hemostasis, and is acceptable. .......................................................... 22
6.1.8 Endpoints and Criteria for Study Success.......................................................... 22
6.1.9 Statistical Considerations & Statistical Analysis Plan .......................................... 22
6.1.10 Study Population and Disposition .................................................................. 22
6.1.11 Efficacy Analyses .......................................................................................... 26
6.1.12 Safety Analyses ............................................................................................ 29
6.1.13 Study Summary and Conclusions ................................................................. 58

9. ADDITIONAL CLINICAL ISSUES ................................................................................. 58
9.1.3 Pediatric Use and PREA Considerations ......................................................... 58

10. CONCLUSIONS ......................................................................................................... 59

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS ...................... 59
11.1 Risk-Benefit Considerations ............................................................................... 59
11.2 Risk-Benefit Summary and Assessment .............................................................. 62
11.4 Recommendations on Regulatory Actions ......................................................... 62
11.5 Labeling Review and Recommendations .......................................................... 63

APPENDIX 1. ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS ................................................................. 64

APPENDIX 2. PEDIATRIC ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS ................................................................. 88
GLOSSARY

AE: adverse event
CI: confidence interval
DSMB: data safety monitoring board
eCRF: electronic case report form
EMA: European Medicines Agency
EU: European Union
EXT: extension
FAS: full analysis set
HBV: hepatitis virus b
HCV: hepatitis virus c
HIV: human immunodeficiency virus
ICF: informed consent form
IND: investigational new drug
MELD: model for end stage liver disease
NAT: nucleic acid testing
OR: odds ratio
PeRC: Pediatric Research Committee
PP: per-protocol analysis set
PREA: Pediatric Research Equity Act
PV B19: parvovirus B19
SAE: serious adverse event
SAF: safety analysis set
SAP: statistical analysis plan
SD: standard deviation
SOC: system organ class
SOP: standard operating procedure
TEAE: treatment-emergent adverse event
1. Executive Summary

Takeda Pharma A/S has submitted STN125351/172, containing the results of Study TC-2402-040-SP, titled, "A Randomized, Open-Label, Parallel Group, Multi-Center Trial to Compare the Efficacy and Safety of TachoSil® versus Surgicel® Original for the Secondary Treatment of Local Bleeding in Adult and Pediatric Patients Undergoing Hepatic Resection Surgery" for the following purposes:

- to expand the labeled TachoSil indication, and
- to fulfil the Pediatric Research Equity Act (PREA) requirement, as stated in the April 5, 2010, TachoSil approval letter.

The sought indication is the following:

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

Limitations for TachoSil Use
- Not for use in place of sutures or other forms of mechanical ligation in treatment of major arterial or venous bleeding.
- Not for use in children under one month of age.

The original action due date of April 20, 2015, was extended to July 20, 2015, after a major amendment (STN125351/172.2) containing immunogenicity data was submitted on November 13, 2014.

**Pediatric Research Equity Act (PREA) Requirement.**

The April 5, 2010, approval letter for TachoSil contained the following statement regarding the PREA requirement:

We are deferring submission of your pediatric study until December 2010 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section
505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for use of TachoSil as an adjunct to hemostasis in pediatric patients 0-16 years undergoing hepatic resection surgery.

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 (see below). 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.

**Study TC-2402-040-SP Design.**
This 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 liver resection surgery. The primary endpoint was the proportion of subjects achieving hemostasis at a pre-identified bleeding site with 3 minutes of study agent application. Secondary endpoints were the proportion of subjects achieving hemostasis within 5 or 10 minutes at the pre-identified bleeding site.

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 Efficacy.

There were 244 adult subjects randomized (114 TachoSil, 110 Surgicel; one subject randomized to Surgicel did not receive the study agent); this referred to as the Full Analysis Set (FAS). Safety was evaluated in the exposed subjects (114 TachoSil, 109 Surgicel); this referred to as the Safety Analysis Set (referenced as 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.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n/N (%)</th>
<th>Exact Binomial 95% CI</th>
<th>Pairwise Comparison TachoSil - Surgicel Original</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio (SE)</td>
</tr>
<tr>
<td>FAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>92/114(80.7)</td>
<td>(72.3, 87.5)</td>
<td></td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>55/110 (50.0)</td>
<td>(40.3, 59.7)</td>
<td>4.87 (1.60)</td>
</tr>
<tr>
<td>PP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>81/99 (81.8)</td>
<td>(72.8, 88.9)</td>
<td></td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>52/99 (52.5)</td>
<td>(42.2, 62.7)</td>
<td>4.83 (1.75)</td>
</tr>
<tr>
<td>Sensitivity Analysis(^1) (FAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

\(^1\) Sensitivity Analysis refers to the analysis of the Full Analysis Set (FAS) after excluding the subject randomized to Surgicel but did not receive the study agent.
Treatment | n/N (%) | Exact Binomial 95% CI | Pairwise Comparison TachoSil - Surgicel Original
---|---|---|---
| | | Odds Ratio (SE) | Wald 95% CI | P value |
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.
Source: STN125352/172 Clinical Report page 117 of 186

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
<th>Exact Binomial CI</th>
<th>Pairwise Comparison TachoSil - Surgical Original</th>
<th>(%</th>
<th>Exact Binomial CI</th>
</tr>
</thead>
</table>
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.
Source: STN125352/172 Clinical Report page 14 of 186

In both adult and pediatric studies, the use of TachoSil resulted in more rapid hemostasis, as shown by the higher proportion of subjects who achieve hemostasis within three minutes at the target bleed site compared to the control group. In the adult study, 80 percent of subjects achieved hemostasis within three minutes, with the lower bound of the 95 percent confidence interval excluding the result for the control group, which was 50 percent achieving hemostasis within three minutes. In the pediatric study, a similar result was observed; however the small sample size limited the statistical analysis.

**Study TC-2402-040-SP Safety.**

The serious and non-serious adverse events for the adult population are shown in **appendix 1**, and for the pediatric population in **appendix 2**.

In the adult study, there were 4 (3.5%) deaths in the TachoSil arm and 7 (6.4%) in the Surgicel arm. In the pediatric study, there was 1 (5%) death in the TachoSil arm and no deaths in the Surgicel arm. All deaths were attributed to the serious underlying medical condition that resulted in liver surgery, or to adverse events associated with liver surgery.

The following table shows the serious adverse events (SAEs) in the adult population that occurred in more than 2 percent of the SAF population:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>TachoSil (N=114)</th>
<th>Surgicel Original (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with at least 1 SAE other than death</td>
<td>43 (37.7)</td>
<td>51 (46.8)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (1.8)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localised intraabdominal fluid</td>
<td>3 (2.6)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>3 (2.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>3 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprocedural bile leak</td>
<td>4 (3.5)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 as 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 condition.

**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.

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.
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 patients. The safety profiles of the adult cardiovascular study, which was used for product licensure, and the adult hepatic resection study in this submission are similar. Although the pediatric hepatic resection study was small, the safety profile was similar to that of the adult hepatic resection study. Therefore, we can extrapolate to conclude that pediatric use is also considered safe for the approved indication, as an adjunct to hemostasis in cardiovascular surgery.

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.

Benefit/Risk Assessment.

Potential risks base on previous observations or mode of action include 1) adverse effects from antibody formation to product components, and 2) potential thrombogenicity. Observed antibody formation has not been associated with adverse effects on safety or efficacy. The potential risk of thrombogenicity has not been observed. Therefore, the risk associated with the use of TachoSil as an adjunct to surgical hemostasis in adult and pediatric patients is small and is out-weighed by the hemostatic benefit. Routine post-marketing surveillance should be sufficient for detection of risks associated with the use of TachoSil.

Recommendation.

STN125351/172 may be approved to add the adjunct to hemostasis indication for adult and pediatric hepatic resection surgery. The pediatric study under protocol TC-2402-040-SP satisfies the PREA requirement for all future adjunct to surgical hemostasis indications. There should be a limitation of use that excludes neonates (less than 30 days of age) because no subjects in this pediatric category were studied.
2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Subjects were undergoing liver resection for a variety of reasons, with bleeding requiring an adjunct to hemostasis.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Tisseel®️, a fibrin sealant, has a general surgical indication. Pharmacologically-unrelated interventions would include Surgicel®, local pressure with gauze pads, and related surgical adjunct to hemostasis techniques.

2.3 Safety and Efficacy of Pharmacologically Related Products

Fibrin Sealant products have been recently reviewed in “Hemostats, Sealants, and Adhesives: A Practical Guide for the Surgeon” [The American Surgeon 78:1305-1321 (2012)].

2.4 Previous Human Experience with the Product (Including Foreign Experience)

TachoComb S (b) (4) TachoSil was approved for marketing in the European Union in June 2004.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

<table>
<thead>
<tr>
<th>Date</th>
<th>Regulatory Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2004</td>
<td>European Commission approved marketing of TachoComb S (b) (4) TachoSil</td>
</tr>
<tr>
<td>September 21, 2004</td>
<td>Type B Pre-BLA meeting (Nycomed, Inc.)</td>
</tr>
<tr>
<td>June 29, 2007</td>
<td>Telecon to discuss required nonclinical studies</td>
</tr>
<tr>
<td>April 1, 2008</td>
<td>Type C meeting to discuss CMC issues</td>
</tr>
<tr>
<td>May 14, 2008</td>
<td>Telecon follow-up to April 1, 2008, meeting</td>
</tr>
<tr>
<td>July 24, 2008</td>
<td>Telecon to discuss clinical development plan</td>
</tr>
<tr>
<td>November 21, 2008</td>
<td>Type B meeting to discuss clinical development plan</td>
</tr>
<tr>
<td>May 29, 2009</td>
<td>STN125351/0 submitted for TachoSil as an adjunct to hemostasis for cardiovascular surgery</td>
</tr>
<tr>
<td>March 10, 2010</td>
<td>Pediatric deferral plan for hepatic surgery (not cardiovascular surgery) submitted to PeRC; PeRC recommended pediatric studies in cardiovascular surgery</td>
</tr>
<tr>
<td>March 15, 2010</td>
<td>Applicant (Nycomed) submitted rationale for conducting hepatic surgery</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>March 31, 2010</td>
<td>PeRC rejected the applicant’s rationale for not doing pediatric cardiovascular studies, but did not make this a requirement.</td>
</tr>
<tr>
<td>April 5, 2010</td>
<td>STN125352/0 approved with deferral of pediatric studies in hepatic surgery</td>
</tr>
<tr>
<td>November 17, 2011</td>
<td>Teleconference to discuss applicant’s difficulties in recruiting pediatric subjects to the hepatic surgery study and a request for delayed time lines</td>
</tr>
<tr>
<td>June 14, 2013</td>
<td>FDA responses to CRMTS #8898 on plans for submitting results of pediatric hepatic surgery study</td>
</tr>
<tr>
<td>November 13, 2014</td>
<td>STN125351/172.2 submitted containing immunogenicity data; declared a major amendment; action due date extended to July 20, 2015</td>
</tr>
<tr>
<td>June 20, 2014</td>
<td>STN125352/172 submitted contain results for the hepatic surgery adjunct to hemostasis indication for adults and pediatric subjects</td>
</tr>
<tr>
<td>June 10, 2015</td>
<td>PeRC presentation for deferred pediatric studies in hepatic surgery</td>
</tr>
<tr>
<td>July 20, 2015</td>
<td>Action Due Date for STN125351/172</td>
</tr>
</tbody>
</table>

The original action due date of April 20, 2015, was extended to July 20, 2015, after a major amendment (STN125351/172.2) containing immunogenicity data was submitted on November 13, 2014.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission lacked basic information, such as narratives for deaths and serious adverse events, and incomplete information on the type of surgical procedures.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The submission appears to be compliant with Good Clinical Practices and Submission Integrity policies.

3.3 Financial Disclosures

<table>
<thead>
<tr>
<th>Covered clinical study (name and/or number): Study TC-2402-040-SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a list of clinical investigators provided: Yes ☒ No ☐ (Request list from applicant)</td>
</tr>
<tr>
<td>Total number of investigators identified: 35</td>
</tr>
</tbody>
</table>
**Number of investigators who are sponsor employees (including both full-time and part-time employees): 0**

**Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0**

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable
- Significant payments of other sorts: Not applicable
- Proprietary interest in the product tested held by investigator: Not applicable
- Significant equity interest held by investigator in sponsor of covered study: Not applicable

**Is an attachment provided with details of the disclosable financial interests/arrangements:** Yes ☑ No ☐ (Request details from applicant)

**Is a description of the steps taken to minimize potential bias provided:** Yes ☑ No ☐ (Request information from applicant)

**Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0**

**Is an attachment provided with the reason:** Yes ☑ No ☐ (Request explanation from applicant)

---

**4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES**

**4.1 Chemistry, Manufacturing, and Controls**

Not applicable – licensed product

**4.2 Assay Validation**

Not applicable

**4.3 Nonclinical Pharmacology/Toxicology**

See nonclinical reviews for STN125351/0

**4.4 Clinical Pharmacology**

Not applicable.
4.4.1 Mechanism of Action

The thrombin/fibrinogen components on the pad form a clot on the matrix of the pad when it is applied to the wound surface.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

See the statistical review for STN125351/172.

4.6 Pharmacovigilance

Not applicable for the review of the submission.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review is based on the adult and pediatric results from the IND study TC-2402-040-SP, conducted under IND 14210.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN 125351/172
- IND 14210
- STN 125351/0 clinical review memo of Kimberly Lindsey, M.D.
5.3 Table of Studies/Clinical Trials

**TABULAR LISTING OF ALL CLINICAL STUDIES**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects (SAF)</th>
<th>Healthy Subjects or Diagnosis of Subjects</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

...
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects (SAF)</th>
<th>Healthy Subjects or Diagnosis of Subjects</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>TC-014-IN</td>
<td>5.3.5.1</td>
<td>Comparison of efficacy and safety of TachoSil versus argon beam coagulator treatment</td>
<td>Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Argon beam coagulator</td>
<td>TachoSil Intraoperative application</td>
<td>121</td>
<td>Subjects requiring elective liver resection for any reason, with minor or moderate hemorrhage persisting after primary surgical hemostatic intervention</td>
<td>Single application</td>
<td>Completed Full report</td>
</tr>
</tbody>
</table>

**Note:** The table contains a summary of the clinical study details for TachoSil (Fibrin Sealant Patch) (Takeda Pharma A/S) as an adjunct to hemostasis for adult and pediatric hepatic resection surgery. The study is designed to compare the efficacy and safety of TachoSil versus argon beam coagulator treatment in a randomized, prospective, multicenter study.
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects (SAF)</th>
<th>Healthy Subjects or Diagnosis of Subjects</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 Efficacy and safety</td>
<td>TC-016-IN</td>
<td>5.3.5.1</td>
<td>Comparison of efficacy and safety of TachoSil versus argon beam coagulator treatment</td>
<td>Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Argon beam coagulator</td>
<td>TachoSil Intraoperative application</td>
<td>119</td>
<td>Subjects requiring elective liver resection for any reason, with only minor or moderate hemorrhage persisting after primary surgical hemostatic procedures of the major vessels</td>
<td>Single application</td>
<td>Completed Full report</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Study Identifier</td>
<td>Location of Study Report</td>
<td>Objective(s) of the Study</td>
<td>Study Design and Type of Control</td>
<td>Test Product(s); Dosage Regimen; Route of Administration</td>
<td>Number of Subjects (SAF)</td>
<td>Healthy Subjects or Diagnosis of Subjects</td>
<td>Duration of Treatment</td>
<td>Study Status; Type of Report</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Phase 4 Safety trial</td>
<td>TC-018-IN</td>
<td>5.3.5.2</td>
<td>Collection of safety information on thromboembolic events, immunological events, and drug interactions leading to thromboembolic events or major bleeding</td>
<td>Prospective, multicenter, noninterventional, single-cohort study</td>
<td>TachoSil Intraoperative application</td>
<td>3098</td>
<td>Subjects prescribed TachoSil in accordance with European label who gave consent for collection of data</td>
<td>Not predefined</td>
<td>Completed Full report</td>
</tr>
<tr>
<td>Phase 3b Single arm Efficacy and safety</td>
<td>TC-019-IN</td>
<td>5.3.5.2</td>
<td>Collection of data on efficacy and safety TachoSil in children.</td>
<td>Prospective, noncomparative, multicenter study</td>
<td>TachoSil Intraoperative application</td>
<td>16</td>
<td>Children &gt;4 weeks and &lt;6 years of age undergoing liver resection with/without segmental liver transplantation</td>
<td>Single application</td>
<td>Completed Full report</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Study Identifier</td>
<td>Location of Study Report</td>
<td>Objective(s) of the Study</td>
<td>Study Design and Type of Control</td>
<td>Test Product(s); Dosage Regimen; Route of Administration</td>
<td>Number of Subjects (SAF)</td>
<td>Healthy Subjects or Diagnosis of Subjects</td>
<td>Duration of Treatment</td>
<td>Study Status; Type of Report</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------</td>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

STN125351/172
TachoSil (Fibrin Sealant Patch) (Takeda Pharma A/S)
as an adjunct to hemostasis for adult and pediatric hepatic resection surgery
Clinical Review Memo – Charles Maplethorpe, MD., Ph.D. CBER/OBRR/DHCR/HPRB
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects (SAF)</th>
<th>Healthy Subjects or Diagnosis of Subjects</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 4 2 arms Efficacy and safety</td>
<td>TC-023-IM</td>
<td>5.3.5.1</td>
<td>Comparison of efficacy and safety of TachoSil versus hemostatic fleece material in cardiovascular surgery</td>
<td>Open, randomized, prospective, multicenter, 2-arm, parallel-group study</td>
<td>TachoSil Intraoperative application</td>
<td>119</td>
<td>Subjects having elective surgery on the heart, the ascending aorta or arch, requiring a cardiopulmonary bypass procedure, and having bleeding from the heart muscle, pericardium, a major vessel or vascular bed that required supportive hemostatic treatment</td>
<td>Single application</td>
<td>Completed Full report</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Study Identifier</td>
<td>Location of Study Report</td>
<td>Objective(s) of the Study</td>
<td>Study Design and Type of Control</td>
<td>Test Product(s); Dosage Regimen; Route of Administration</td>
<td>Number of Subjects (SAF)</td>
<td>Healthy Subjects or Diagnosis of Subjects</td>
<td>Duration of Treatment</td>
<td>Study Status; Type of Report</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------</td>
<td>--------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Phase 3 Efficacy and Safety</td>
<td>TC-026-JP</td>
<td>5.3.5.1</td>
<td>Comparison of efficacy and safety of TachoSil versus TachoComb</td>
<td>Multicenter, double-blind, randomized, comparative, noninferiority study Control: TachoComb</td>
<td>TachoSil</td>
<td>111</td>
<td>Subjects undergoing elective liver resection</td>
<td>Single application</td>
<td>Completed Full report</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Study Identifier</td>
<td>Location of Study Report</td>
<td>Objective(s) of the Study</td>
<td>Study Design and Type of Control</td>
<td>Test Product(s); Dosage Regimen; Route of Administration</td>
<td>Number of Subjects (SAF)</td>
<td>Healthy Subjects or Diagnosis of Subjects</td>
<td>Duration of Treatment</td>
<td>Study Status; Type of Report</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------</td>
<td>------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

Source: STN125351/172 Clinical Report Section 2.7.6
5.4 Consultations

None

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable

5.4.2 External Consults/Collaborations

None

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 Study TC-2402-040-SP “A randomized, open label, parallel-group, multi-center trial to compare the efficacy and safety of TachoSil® versus Surgicel® Original for the secondary treatment of local bleeding in adult and pediatric patients undergoing hepatic resection surgery.”

6.1.1 Objectives (Primary, Secondary, etc)

- to show that TachoSil was superior to Surgicel Original as secondary hemostatic treatment after hepatic resection surgery and primary hemostatic treatment in adult patients
- safety of TachoSil as secondary hemostatic treatment in hepatic resection surgery
- to explore the efficacy and safety of TachoSil as secondary hemostatic treatment in hepatic resection surgery in pediatric patients.

6.1.2 Design Overview

Randomized (1:1), open-label, parallel-group, multicenter in adults and pediatric subjects undergoing liver surgery
TachoSil or standard hemostatic (comparator) treatment. (b) Hemostasis in studies TC-014-IN, TC-016-IN, TC-2402-040-SP (adults and pediatric) and TC-019-IN was assessed at 3 to 10 minutes after the first application of test treatment (ie, the secondary hemostatic treatment). Hemostasis in study TC-023-IM was assessed at 3 and 6 minutes after the first application of test treatment (ie, the secondary hemostatic treatment).

Source: STN125352/172 module 2.6 Clinical Overview p. 14 of 47

**Reviewer Comment:** This is a standard design for fibrin sealant adjunct to surgical hemostasis studies, and is acceptable.

### 6.1.3 Population

The subjects were adults or pediatric patients (age 0 to 18 years of age) undergoing elective hepatectomy of at least one anatomical segment of the liver for any medical reason. Subjects needed to demonstrate mild to moderate (oozing/diffuse) bleeding from the resection area after primary control of arterial or venous bleeding by conventional measures. Subjects were excluded for coagulopathy (investigator’s discretion), hypersensitivity to product components (human fibrinogen, human thrombin and/or collagen of any type), drug or alcohol abuse, or participation in another investigational study within 30 days of enrollment, among other conventional exclusions.

**Reviewer Comment:** The study population is acceptable.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

1. TachoSil, an equine collagen patch coated with the fibrin glue components: human fibrinogen and human thrombin
2. Surgicel Original absorbable hemostat (oxidized regenerated cellulose)
6.1.5 Directions for Use

The hemostatic patches are cut-to-size as needed.

6.1.6 Sites and Centers

<table>
<thead>
<tr>
<th>Site No</th>
<th>Principal Investigator</th>
<th>Site Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-4001</td>
<td>William C. Chapman</td>
<td>Washington University School of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>660 South Euclid Ave, Campus Box 8109</td>
</tr>
<tr>
<td></td>
<td></td>
<td>St Louis, MO 63110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Center for Advanced Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4921 Parkview Place</td>
</tr>
<tr>
<td></td>
<td></td>
<td>St Louis, MO 63110</td>
</tr>
<tr>
<td>US-4002</td>
<td>James D. Eason</td>
<td>James D. Eason, MD, FACS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1211 Union Ave, Ste 340</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Memphis, TN 38104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methodist University Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1265 Union Ave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Memphis, TN 38104</td>
</tr>
<tr>
<td>US-4003</td>
<td>Thomas Fishbein</td>
<td>Georgetown University Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Main – Transplant Institute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3800 Reservoir Rd NW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Washington, DC 20007</td>
</tr>
<tr>
<td>US-4004</td>
<td>David Anthony Iannitti</td>
<td>Carolinas Medical Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of General Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1025 Morehead Medical Dr, Ste 300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Charlotte, NC 28204</td>
</tr>
</tbody>
</table>
Enrollment of Adult Patients

<table>
<thead>
<tr>
<th>Site No</th>
<th>Principal Investigator</th>
<th>Site Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-4005</td>
<td>David Imagawa</td>
<td>University of California Irvine Medical Center – 101 The City Drive Orange, CA 92868</td>
</tr>
<tr>
<td>US-4007</td>
<td>James John Pomposelli</td>
<td>Lahey Clinic 41 Mall Rd Burlington, MA 01805</td>
</tr>
<tr>
<td>US-4008</td>
<td>Charles Raben Scoggins</td>
<td>314 E. Broadway, #303 Louisville, KY 40202</td>
</tr>
<tr>
<td></td>
<td></td>
<td>University of Louisville Hospital 530 S. Jackson St Louisville, KY 40202</td>
</tr>
<tr>
<td>US-4009</td>
<td>Linda S. Sher</td>
<td>Division of Hepatobiliary Pancreatic Surgery and Abdominal Organ Transplantation Keck Medical Center of USC HCC 1, Ste 200 1510 San Pablo St Los Angeles, CA 90033</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keck Hospital, USC</td>
</tr>
<tr>
<td>US-4010</td>
<td>Douglas Philip Slakey</td>
<td>Tulane University School of Medicine Department of Surgery 1430 Tulane Ave New Orleans, LA 70112</td>
</tr>
<tr>
<td>Site No</td>
<td>Principal Investigator</td>
<td>Site Address</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>US-4011</td>
<td>Gary S. Xiao</td>
<td>Drexel University College of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi-Organ Transplant and Hepatobiliary Pancreato Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>216 N Broad St, 5th Floor, Feinstein Bldg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Philadelphia, PA 19102</td>
</tr>
<tr>
<td>US-4012</td>
<td>Tomoaki Kato</td>
<td>Columbia University Medical Center (CUMC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>622 West 168th St, 14th Floor, Ste 105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New York, NY 10032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Center for Liver Disease and Transplantation, CUMC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>622 W 168th St, PH-14 Clinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New York, NY 10032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CUMC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177 Fort Washington Ave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New York, NY 10032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children’s Hospital of New York</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3959 Broadway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New York, NY 10032</td>
</tr>
<tr>
<td>US-4014</td>
<td>Ervin Steve Woodle</td>
<td>University of Cincinnati College of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>231 Albert Sabin Way, ML 0558</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cincinnati, OH 45267</td>
</tr>
<tr>
<td>US-4015</td>
<td>Reid Barton Adams</td>
<td>University of Virginia Health System</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1300 Jefferson Park Ave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Charlottesville, VA 22903</td>
</tr>
<tr>
<td>Site No</td>
<td>Principal Investigator</td>
<td>Site Address</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>US-4016</td>
<td>Myron Eliot Schwartz</td>
<td>Mount Sinai School of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1425 Madison Ave, Suite L4-66,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Box 1104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New York, NY 10029</td>
</tr>
<tr>
<td>US-4017</td>
<td>James Michael Millis</td>
<td>University of Chicago Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5841 South Maryland Ave, MC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chicago, IL 60637</td>
</tr>
<tr>
<td>US-4018</td>
<td>John Kelly Wright, Jr.</td>
<td>Vanderbilt University Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1211 Medical Center Dr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nashville, TN 37232</td>
</tr>
<tr>
<td>US-4019</td>
<td>Sharon Marie Weber</td>
<td>University of Wisconsin Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and Clinics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 Highland Ave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Madison, WI 53792</td>
</tr>
<tr>
<td>US-4020</td>
<td>Barburao Koneru</td>
<td>UMDNJ Division of Transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>185 South Orange Ave, G 536</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Newark, NJ 07101</td>
</tr>
<tr>
<td>US-4021</td>
<td>Kenneth David Chavin</td>
<td>Medical University of South</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carolina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Transplant Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96 Jonathan Lucas St, CSB 409</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Charleston, SC 29425</td>
</tr>
</tbody>
</table>
## Enrollment of Pediatric Patients

<table>
<thead>
<tr>
<th>Site No</th>
<th>Principal Investigator</th>
<th>Site Address</th>
</tr>
</thead>
</table>
| US-4003| Thomas Fishbein              | Georgetown University Hospital  
2 Main – Transplant Institute  
3800 Reservoir Rd NW Washington, DC 20007 |
| US-4012| Tomoaki Kato                 | Columbia University Medical Center (CUMC)  
622 West 168th St, 14th Floor, Ste 105  
New York, NY 10032  
Center for Liver Disease and Transplantation, CUMC  
622 W 168th St, PH-14 Clinic  
New York, NY 10032 |
| US-4021| Kenneth David Chavin         | Medical University of South Carolina  
Department of Transplant Surgery  
96 Jonathan Lucas St, CSB 409  
Charleston, SC 29425  
Medical University of South Carolina Transplant Clinic  
135 Rutledge Ave, 9th Floor Clinic  
Charleston, SC 29425 |
| US-4022| Yuri Genyk                   | Children’s Hospital Los Angeles  
4650 Sunset Blvd  
Los Angeles, CA 90027  
Division of Abdominal Organ Transplantation  
Health Care Consultation 1  
1510 San Pablo St, Ste 200  
Los Angeles, CA 90033 |
Enrollment of Pediatric Patients

<table>
<thead>
<tr>
<th>Site No</th>
<th>Principal Investigator</th>
<th>Site Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-4023</td>
<td>Riccardo Superina</td>
<td>Ann and Robert H. Lurie Children’s Hospital of Chicago 225 East Chicago Ave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chicago, IL 60611</td>
</tr>
</tbody>
</table>

6.1.7 Surveillance/Monitoring

Trial Flow Chart

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening (Day -42 to Day 1)[1]</th>
<th>Baseline (Day -1 or Day 1 prior to randomization/ TRIAL TREATMENT)</th>
<th>Day of Surgery (Day 1)</th>
<th>Daily assessments until discharge</th>
<th>Discharge from surgical ward</th>
<th>Follow-up (1 month ± 10 days)</th>
<th>Follow-up (3 months ± 10 days)</th>
<th>Follow-up (6 months ± 10 days)[8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>X</td>
<td>[2] [2] X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned procedures</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
### Procedures

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening (Day -42 to Day 1) [1]</th>
<th>Baseline (Day -1 or Day 1 prior to randomization/ Trial Treatment)</th>
<th>Day of Surgery (Day 1)</th>
<th>Daily assessments until discharge</th>
<th>Discharge from surgical ward</th>
<th>Follow up (1 month ± 10 days)</th>
<th>Follow up (3 months ± 10 days)</th>
<th>Follow up (6 months ± 10 days) [8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test (urine or blood)</td>
<td>X[2]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology and blood chemistry [5]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sampling for immunogenicity testing [6,7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral serology testing [6,7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization [7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug accountability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>End of trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

[1] Screening and/or Baseline and/or Day of Surgery procedures were done on the same day, but all Screening and Baseline procedures were done prior to randomization
[2] Pregnancy test was done at Baseline; exclusion criterion was considered
[3] After Baseline visit, only follow-up/resolution of documented concomitant illness
[4] Height/length without shoes and body weight were only recorded at Screening. On Day of Surgery, vital signs were recorded before surgery
[5] Hematology: blood hemoglobin, complete blood count, erythrocytes, leukocytes (lymphocytes, neutrophils, eosinophils, basophils, monocytes) and platelets; blood chemistry: prothrombin time, activated partial thromboplastin, international
Source: STN125351/172 Clinical Report page 59 or 186

_Reviewer Comment:_ The monitoring plan is standard for fibrin sealants for use as an adjunct to surgical hemostasis, and is acceptable.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was hemostasis at the target bleeding site (i.e. the bleed site identified during surgery for primary endpoint evaluation) within 3 minutes of application of the hemostatic study agent in the ITT population.

Secondary endpoints included the following:
- Hemostasis at the target bleed site within 5 minutes of application of the study agent
- Hemostasis at the target bleed site within 10 minutes of application of the study agent

6.1.9 Statistical Considerations & Statistical Analysis Plan

The following considerations entered into the statistical analysis plan:
- centers with small enrollment were pooled
  - if all or none of the subjects at the center achieved the primary endpoint
  - if the center enrolled fewer than 6 subjects
- center pooling fulfilled the following criteria:
  - geographic proximity
  - within same time zone and hospital type (public or private)
- For all logistic regression analyses, the Wald 95% confidence intervals is obtained from the model and presented for the odds ratios.
  - Exact binomial 95% confidence intervals are obtained for any raw proportions presented. P-values are based on the Wald test.
- Analysis sets are as follows:
  - ‘Full Analysis Set’ (FAS) is used to describe the analysis set which is as complete as possible and as close to the intent-to-treat ideal of including all randomized subjects
  - Per-protocol analysis set (PP) defines a subset of randomized patients who are considered compliant with the protocol.
  - Safety analysis set (SAF) will be defined as all patients who are randomized and exposed to trial treatment.

6.1.10 Study Population and Disposition
6.1.10.1 Populations Enrolled/Analyzed

The outcomes were analyzed for the Intent-to-Treat population (the ‘full analysis set’ or subjects as randomized), the per-protocol population (protocol compliant subjects), and the safety analysis population (all subjects as treated). The following table shows subject disposition within these analysis populations:

### Analysis Populations for Adult Patients at Baseline

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>TachoSil (N=114)</th>
<th>Surgicel Original (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>114 (100)</td>
<td>110 (100)</td>
</tr>
<tr>
<td>PP</td>
<td>99 (86.8)</td>
<td>99 (90.0)</td>
</tr>
<tr>
<td>SAF</td>
<td>114 (100)</td>
<td>109 (99.1)</td>
</tr>
</tbody>
</table>

FAS, full analysis set; N, total number of patients in group; n, the number of patients within the analysis set; PP, per-protocol analysis set; SAF, safety analysis set.

The enrolled total includes all patients enrolled in the trial, including those who were not randomly assigned. A patient was considered enrolled if they were given a patient ID number and had given informed consent.

Source: STN125352/172 Clinical Report p. 97 of 186

6.1.10.1.1 Demographics

The following table shows the adult and pediatric distribution of the enrollment across sex and race categories:

### Study TC-2402-040-SP Demographic by Treatment and Age Group

<table>
<thead>
<tr>
<th>RACE</th>
<th>SEX</th>
<th>Surgicel Pediatric (&lt; 18 y.o)</th>
<th>Surgicel Adult</th>
<th>TachoSil Pediatric (&lt; 18 y.o)</th>
<th>TachoSil Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>Female</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Black or African American</td>
<td>Female</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Multiple</td>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>Female</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>6</td>
<td>56</td>
<td>14</td>
<td>60</td>
</tr>
</tbody>
</table>
### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

<table>
<thead>
<tr>
<th>RACE</th>
<th>SEX</th>
<th>Surgicel Pediatric (&lt; 18 y.o)</th>
<th>Surgicel Adult</th>
<th>TachoSil Pediatric (&lt; 18 y.o)</th>
<th>TachoSil Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>3</td>
<td>27</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3</td>
<td>29</td>
<td>8</td>
<td>32</td>
</tr>
</tbody>
</table>

Source: Analysis of data in STN125351/172 database ADDM

### 6.1.10.1.3 Subject Disposition
Figure 2  Disposition of Patients - All Adult Patients Enrolled

Discontinued at Baseline:
N = 97
Reasons (n):
  - withdrawal of consent (7)
  - AE prior to randomization (1)
  - not eligible (60)
  - other (29)

N = 321 Enrolled

N = 224 Randomized and FAS

N = 114 TachoSil®

Discontinued at Any Time During Trial:
N = 13
Reasons:
  - withdrawal of consent (3)
  - lost to follow-up (4)
  - AE (1)
  - fatal AE (4)
  - other (1)

Day of Discharge:
  - fatal AE (1)

Daily Assessments:
  - fatal AE (1)

At 1-Month Follow-up
  - withdrawal of consent (3)
  - lost to follow-up (3)
  - fatal AE (1)

At 3-Month Follow-up
  - lost to follow-up (1)
  - AE (1)
  - fatal AE (1)
  - Other (1)

N = 101 completed

N = 110 Surgicel® Original

Discontinued at Any Time During Trial:
N = 11
Reasons:
  - withdrawal of consent (1)
  - lost to follow-up (2)
  - AE (0)
  - fatal AE (6)
  - other (2)

Day of Surgery:
  - fatal AE (1)

Daily Assessments:
  - fatal AE (1)

At 1-Month Follow-up
  - fatal AE (2)
  - Other (1)

At 3-Month Follow-up
  - withdrawal of consent (1)
  - lost to follow-up (2)
  - fatal AE (2)
  - Other (1)

N = 99 completed

AE, adverse event; FAS, full analysis set.

* One additional patient in the Surgicel Original group (Patient 4007018) had a fatal AE but was not recorded as discontinuing due to this AE because the date of death (b) (6) was after the date the patient completed the trial (07 September 2012).

Source: STN125352/172 Clinical Report p. 91 of 186
6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The full analysis set (FAS) consisted of 144 subjects in the TachoSil arm, and 110 subjects in the Surgicel control arm. All these subjects, except one subject in the Surgicel arm, were included in the safety analysis set (SAF). The per protocol (PP) set excluded 15 subjects from the TachoSil arm, and 11 subjects from the Surgicel arm, leaving 99 subjects in the TachoSil PP set, and 99 subjects in the Surgicel PP set.
Logistic Regression Models of Proportion of Adult Patients With Hemostasis Within 3 Minutes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n/N (%)</th>
<th>Exact Binomial 95% CI</th>
<th>Pairwise Comparison</th>
<th>Odds Ratio (SE)</th>
<th>Wald 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>92/114</td>
<td>(72.3, 87.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>55/110</td>
<td>(40.3, 59.7)</td>
<td>4.87 (1.60)</td>
<td>(2.55, 9.29)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(50.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>81/99 (81.8)</td>
<td>(72.8, 88.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>52/99 (52.5)</td>
<td>(42.2, 62.7)</td>
<td>4.83 (1.75)</td>
<td>(2.37, 9.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(52.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity Analysis</strong> (FAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>92/114</td>
<td>(72.3, 87.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>56/110</td>
<td>(41.2, 60.6)</td>
<td>4.73 (1.56)</td>
<td>(2.47, 9.03)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(50.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set; SE, standard error. Percentages are based on the number of patients with time to hemostasis in the FAS. The proportion of patients 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.

Source: STN125352/172 Clinical Report page 117 of 186

6.1.11.2 Analyses of Secondary Endpoints

Logistic Regression Models of Proportion of Adult Patients with Hemostasis within 5 Minutes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n/N (%)</th>
<th>Exact</th>
<th>Pairwise Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Binomial 95% CI</td>
<td>Odds Ratio (SE)</td>
<td>Wald 95% CI</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>FAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>108/114 (88.9, 98.0)</td>
<td>6.24 (3.06)</td>
<td>(2.39, 16.30)</td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>84/110 (76.4, 83.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TachoSil</td>
<td>96/99 (97.0, 99.4)</td>
<td>10.03 (6.57)</td>
<td>(2.78, 36.19)</td>
</tr>
<tr>
<td>Surgicel Original</td>
<td>78/99 (78.8, 86.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set; SE, standard error. Percentages are based on the number of patients with time to hemostasis in the FAS. The proportion of patients with hemostasis within 5 minutes was analyzed by using a logistic regression model with treatment and pooled center as covariates.

1. P value was adjusted using Hochberg’s adjustment for multiplicity (see Section 9.7.1.4.1.4 for details). P values are 2-sided.

Source: STN125532/172 Clinical Report page 120 of 3301

### 6.1.11.4 Dropouts and/or Discontinuations

The primary efficacy analysis was repeated by imputing all missing values as having hemostasis at 3 minutes. A conservative sensitivity analysis for the primary efficacy analysis of the primary efficacy endpoint was conducted, where missing values in the Surgicel Original group were counted as having hemostasis within 3 minutes and those in the TachoSil group were counted as not having hemostasis within 3 minutes.
6.1.12 Safety Analyses

6.1.12.1 Methods

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>TachoSil (N=114)</th>
<th>Surgicel Original (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>E</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total number of patients with at least 1 adverse event of special interest</td>
<td>42 (36.8)</td>
<td>69</td>
<td>55 (50.5)</td>
</tr>
<tr>
<td>Adhesions (including bowel obstruction)</td>
<td>33 (28.9)</td>
<td>42</td>
<td>37 (33.9)</td>
</tr>
<tr>
<td>Serious</td>
<td>8 (7.0)</td>
<td>8</td>
<td>11 (10.1)</td>
</tr>
<tr>
<td>Nonserious</td>
<td>26 (22.8)</td>
<td>34</td>
<td>30 (27.5)</td>
</tr>
<tr>
<td>Hepatic abscess or other surgically related infections</td>
<td>15 (13.2)</td>
<td>19</td>
<td>20 (18.3)</td>
</tr>
<tr>
<td>Serious</td>
<td>11 (9.6)</td>
<td>12</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Nonserious</td>
<td>7 (6.1)</td>
<td>7</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Surgically related thromboembolic events</td>
<td>4 (3.5)</td>
<td>8</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>2 (1.8)</td>
<td>3</td>
<td>10 (9.2)</td>
</tr>
<tr>
<td>Nonserious</td>
<td>2 (1.8)</td>
<td>5</td>
<td>7 (6.4)</td>
</tr>
</tbody>
</table>

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; %, number of patients with at least 1 event as % of the SAF; SAF, safety analysis set.

Adverse event terms were coded using the Medical Dictionary for Regulatory Activities, Version 15.1.

Source: STN125351/172 clinical report page 150 of 3301

Summary of Adverse Events of Special Interest in Pediatric Patients by Treatment (SAF)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>TachoSil (N=20)</th>
<th>Surgicel Original (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>E</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total number of patients with at least 1 adverse event of special interest</td>
<td>6 (30.7)</td>
<td>12</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>TachoSil (N=20)</td>
<td>Surgicel Original (N=9)</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>Preferred Term</td>
<td>n (%)</td>
<td>E</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adhesions (including bowel obstruction)</td>
<td>5 (25.0)</td>
<td>6</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Serious</td>
<td>3 (15.0)</td>
<td>3</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Nonserious</td>
<td>3 (15.0)</td>
<td>3</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Hepatic abscess or other surgically related infections</td>
<td>1 (5.0)</td>
<td>1</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Nonserious</td>
<td>1 (5.0)</td>
<td>1</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Surgically related thromboembolic events</td>
<td>2 (10.0)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Serious</td>
<td>2 (10.0)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nonserious</td>
<td>1 (5.0)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; %, number of patients with at least 1 event as % of the SAF; SAF, safety analysis set.

Adverse event terms were coded using the Medical Dictionary for Regulatory Activities, Version 15.1.
Source: STN125351/172 clinical report page 151 of 3301

6.1.12.2 Overview of Adverse Events

6.1.12.3 Deaths

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, multiorgan failure, and hepatic failure. The pediatric death was in a 6 month old female who experienced disseminated intravascular coagulopathy with exsanguination after septicemia.

Reviewer Comment: All deaths appear to be related to the underlying medical condition.

Study TC-2402-040-SP: Deaths of Adult Subjects – Narrative and Serious Adverse Events

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
<th>Narrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td></td>
<td></td>
<td></td>
<td>This case concerns a 57 year old female subject who experienced a fatal serious adverse event of</td>
</tr>
</tbody>
</table>
### Patient ID | Study Arm | AE Onset Study Day | Adverse Event (AE) | Outcome |
--- | --- | --- | --- | --- |
4001015 | Surgicel | -6 | Granulomatous disease in spleen | Not Recovered |
4001015 | Surgicel | 1 | Periods of apnea | Recovered |
4001015 | Surgicel | 1 | Hyperglycemia | Recovered |
4001015 | Surgicel | 2 | Oliguria | Recovered |
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>2</td>
<td>intermittent tachycardia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>3</td>
<td>post right liver trisectionectomy Bile duct leak</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>4</td>
<td>Red rash on abdomen</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>4</td>
<td>Red rash on left thigh</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>5</td>
<td>Nausea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>6</td>
<td>bilateral pleural effusions</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>8</td>
<td>Constipation</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>10</td>
<td>left arm edema</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>11</td>
<td>ecchymosis of left upper extremity</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>15</td>
<td>Weakness</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>15</td>
<td>Dizziness</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>15</td>
<td>Chills</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>15</td>
<td>Thrombocytopenia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hyponatremia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Febrile</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Proteinuria</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Elevated BUN</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hypoclamia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Left basilar atelectasis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hypotension</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>intermittent Tachycardia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>worsening anemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Study Arm</td>
<td>AE Onset Study Day</td>
<td>Adverse Event (AE)</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>16</td>
<td>massive Gastrointestinal bleed</td>
<td>FATAL</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>17</td>
<td>superior mesenteric vein thrombus</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>17</td>
<td>Hematemesis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>18</td>
<td>Hypercoagulation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>20</td>
<td>Diffuse colitis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>20</td>
<td>Pelvic free fluid</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>20</td>
<td>Melanic stool</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>21</td>
<td>Partially contained dissection flap within the common hepatic artery</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>21</td>
<td>Vascular procedure complication/ Hyperkalemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>21</td>
<td>Anxiety</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>21</td>
<td>Shortness of breath</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001015</td>
<td>Surgicel</td>
<td>21</td>
<td>Hypoxia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td></td>
<td>This case concerns a 54 year old female subject who experienced fatal serious adverse events of abdominal abscess and sepsis. This subject underwent resection for cell carcinoma of gallbladder and liver on (Study Day 1). The subject was randomized to the comparator treatment for secondary treatment of hemostasis. On Study Day 13, the subject was admitted from another hospital with abdominal abscess. Treatment with ciprofloxacin, doripenem, micafungin and vancomycin had been given for the abscess. Drainage revealed 1000 ml purulent fluid.</td>
<td></td>
</tr>
</tbody>
</table>

This case concerns a 54 year old female subject who experienced fatal serious adverse events of abdominal abscess and sepsis. This subject underwent resection for cell carcinoma of gallbladder and liver on (Study Day 1). The subject was randomized to the comparator treatment for secondary treatment of hemostasis. On Study Day 13, the subject was admitted from another hospital with abdominal abscess. Treatment with ciprofloxacin, doripenem, micafungin and vancomycin had been given for the abscess. Drainage revealed 1000 ml purulent fluid.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td>21</td>
<td>peripheral edema</td>
<td>Recovered</td>
</tr>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td>21</td>
<td>abdominal pain</td>
<td>Recovered</td>
</tr>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td>21</td>
<td>radiating right shoulder pain</td>
<td>Recovered</td>
</tr>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td>23</td>
<td>abdominal abscess</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4002005</td>
<td>Surgicel</td>
<td>24</td>
<td>sepsis</td>
<td>FATAL</td>
</tr>
</tbody>
</table>

This case concerns a 77 year-old male subject who experienced a fatal serious adverse event of metastases to bone, and nonfatal serious adverse events of abdominal abscess, pleural effusion, and jaundice. This subject underwent a right hepatectomy on (Study Day 1). The subject was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. The subject was re-admitted to the hospital due to weight loss and abnormal white blood count (WBC values), and was subsequently diagnosed with abdominal abscess on Study Day 35. On Study Day 49, the event of bilateral pleural effusion was diagnosed. On Study Day 49, new lesions were identified on CT scan and metastases to bone was reported. The subject recovered from abdominal abscess on Study Day 58. The subject was re-admitted on Study Day 64 for new onset of jaundice. The outcome for the events of pleural effusion and jaundice are unknown. Care was withdrawn on Study Day 80 when the subject died due to progression of cancer. The investigator considered the events to be not related to trial drug but due to operative complication.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>1</td>
<td>atrial fibrillation</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>1</td>
<td>dehydration</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>1</td>
<td>elevated liver enzymes</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>1</td>
<td>weight loss</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>urticaria</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>hypotension</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>thrombocytopenia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>acute kidney injury</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>bibasilar atelectasis</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>hyperkalemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>Dehydration</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>2</td>
<td>bilateral pleural effusion</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>3</td>
<td>hepatic steatosis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>7</td>
<td>melena</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>20</td>
<td>fatigue</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>35</td>
<td>abdominal abscess</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>35</td>
<td>loss of appetite</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>35</td>
<td>loss of mental acuity</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>35</td>
<td>failure to thrive</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>35</td>
<td>acute fatigue</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>dehydration</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>Carbohydrate antigen 19-9 increased/</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>depression</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>Elevated White Blood Cell Count</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>

Narrative: to study drug but due to progression of underlying disease.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>Recurrent bilateral atelectasis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>pulmonary nodules</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>renal cysts</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>49</td>
<td>bowel wall thickening, terminal ileum</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>50</td>
<td>hypokalemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>57</td>
<td>progression of disease-metastasis to bone</td>
<td>FATAL</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>58</td>
<td>nausea</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>58</td>
<td>1.5 cm lucency t9 vertebral body on imaging</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>Cough</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>dehydration</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>jaundice</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>confusion</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>Hyperbilirubinemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>pedal edema</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>joint pain</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>64</td>
<td>abdominal pain</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>68</td>
<td>atrial fibrillation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>72</td>
<td>Constipation</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>76</td>
<td>Acute Respiratory Failure</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>76</td>
<td>lower nephron nephrosis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4003001</td>
<td>Surgicel</td>
<td>78</td>
<td>acidosis</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>
This case concerns a 70 year-old female subject who experienced a fatal serious adverse event of recurrent hepatic cancer, and nonfatal serious adverse events of wound infection staphylococcal and staphylococcus test positive. This subject underwent uncomplicated liver lobectomy due to hepatocellular carcinoma on (Study Day 1). The subject was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. On Study Day 36, the subject was seen in the emergency department due to fatigue and fever. Blood cultures had returned positive for methicillin resistant staphylococcus aureus and a worsening of the wound infection was reported. The subject was considered stable and was discharged home with oral antibiotics (sulfamethoxazole/trimethoprim and cephalexin). The event of staphylococcus positive resolved on Study Day 40 and the wound infection resolved on Study Day 112. The subject died on Study Day 137 due to recurrence of hepatocellular carcinoma. The investigator considered the events as not related to Surgicel; an alternative etiology was not provided.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>1</td>
<td>Elevated White Blood Cell Count</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>1</td>
<td>worsening anemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>1</td>
<td>atelectasis</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>1</td>
<td>bilateral pleural effusions</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>2</td>
<td>fever</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>3</td>
<td>Mild Confusion</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>4</td>
<td>acidemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>4</td>
<td>retaining oxygen</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>5</td>
<td>Post Operative weakness</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>20</td>
<td>Wound infection</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>20</td>
<td>bilateral pedal edema</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>34</td>
<td>fatigue</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>36</td>
<td>Positive Blood Culture</td>
<td>Recovered</td>
</tr>
</tbody>
</table>
### Adverse Events

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>36</td>
<td>Recurrent wound infection, MRSA</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>38</td>
<td>yeast infection</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>63</td>
<td>nausea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4003012</td>
<td>Surgicel</td>
<td>137</td>
<td>Hepatic neoplasm malignant recurrent</td>
<td>FATAL</td>
</tr>
</tbody>
</table>

#### 4007018

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Narrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgicel</td>
<td>This case concerns a 75 year-old male subject who experienced a fatal serious adverse event of cholangitis, and nonfatal serious adverse events of bacteremia (twice), cholangitis, bile duct stenosis, and renal failure. This subject underwent liver surgery on <a href="#">Study Day 1</a>. The patient was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. On Study Day 83, the subject developed bacteremia. Interventional antibiotic therapy was initiated and the subject recovered on Study Day 85. The investigator considered the event to be not related to study drug but due to bile duct stricture and cancer. On Study Day 97, the subject developed cholangitis. Following the scheduled Percutaneous Transhepatic Cholangiography, the subject was fully recovered on Study Day 98 and was discharged. The investigator considered the event to be not related to study drug but due to the underlying disease of stage IV gallbladder carcinoma. On Study Day 149, the subject once again developed bacteremia. Interventional therapy with antibiotics was initiated on Study Day 149. On Study Day 151, the subject was hospitalized and subjected to intravenous administration of vancomycin as interventional therapy. The event was considered recovered on Study Day 154. The investigator considered the event to be not related to study drug but an otherwise unspecified underlying disease of fevers. On Study Day 170, the subject developed recurrent</td>
</tr>
</tbody>
</table>
cholangitis. The subject was treated with intravenous antibiotics. The investigator considered the event to be not related to study drug but due to underlying diseases rigors, malaise, and abdominal pain (not further specified). On Study Day 190, the subject developed bile duct stenosis and, on Study Day 195, acute kidney injury leading to renal failure. Treatment with sodium chloride and albumin were initiated on Study Days 190 and 198, respectively. The subject was discharged to hospice on Study Day 203 and died on Study Day 204. The investigator reported that the subject had not recovered from the events of bile duct stenosis and renal failure at the time of death. The investigator considered the acute kidney injury leading to renal failure not related to study treatment and put forward atrial fibrillation as an alternative etiology.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>1</td>
<td>Dizziness</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>2</td>
<td>Forgetfulness</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>2</td>
<td>Agitated</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>15</td>
<td>Bile Duct Stricture</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>83</td>
<td>Bacteremia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>97</td>
<td>Cholangitis</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>149</td>
<td>bacteremia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>170</td>
<td>recurrent cholangitis</td>
<td>FATAL</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>190</td>
<td>Malignant Biliary Stricture</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4007018</td>
<td>Surgicel</td>
<td>195</td>
<td>Acute Kidney Injury Leading to Renal Failure</td>
<td>Not Recovered</td>
</tr>
<tr>
<td><strong>4021015</strong></td>
<td><strong>Surgicel</strong></td>
<td><strong>82 y.o. female</strong></td>
<td><strong>Liver surgery for cancer</strong></td>
<td><strong>This case concerns an 82 year old female subject who experienced a fatal serious adverse event of acute myocardial infarction. This subject underwent liver surgery on (Study Day 1). The subject was randomized to the comparator treatment for secondary hemostasis. The subject had a normal post-operative recovery. On the same day of surgery, the subject developed acute myocardial infarction. Four hours after surgery</strong></td>
</tr>
</tbody>
</table>
the subject developed cardiorespiratory arrest. Resuscitation with intubation, compression and defibrillation took place for 45 minutes. The subject went to the Intensive Care Unit (ICU) where it continued for additional 40 minutes. The subject was brought back to surgery for re-exploration and death was pronounced on Study Day one at 06:15 PM. According to the autopsy report, the probable death cause was acute myocardial infarction due to severe atherosclerotic coronary artery disease complicated by extensive pulmonary tumor embolic disease due to hepatocellular carcinoma. The autopsy also revealed that the subject had a medical history of coronary artery disease. The subject died from the acute myocardial infarction on the same day. The subject’s medical history of coronary artery disease presents a possible alternative etiology for acute myocardial infarction. The event of acute myocardial infarction is considered by the investigator to be not related to study treatment, and related to the postoperative course as a complication.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>-6</td>
<td>Granulomatous disease in spleen</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>1</td>
<td>Periods of apnea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>1</td>
<td>Hyperglycemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>2</td>
<td>Intermittent tachycardia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>3</td>
<td>Bile duct leak</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>4</td>
<td>Oliguria</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>4</td>
<td>Red rash on abdomen</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>4</td>
<td>Red rash on left thigh</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>5</td>
<td>Nausea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>6</td>
<td>Bilateral pleural effusions</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>8</td>
<td>Constipation</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>10</td>
<td>Left arm edema</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>11</td>
<td>Ecchymosis of left upper extremity</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Study Arm</td>
<td>AE Onset Study Day</td>
<td>Adverse Event (AE)</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>15</td>
<td>Weakness</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>15</td>
<td>Dizziness</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>15</td>
<td>Chills</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hyponatremia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Febrile</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Thrombocytopenia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Proteinuria</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Elevated BUN</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hypoclamia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Left basilar atelectasis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>Hypotension</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>intermittent Tachycardia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>worsening anemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>16</td>
<td>massive Gastrointestinal bleed</td>
<td>FATAL</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>17</td>
<td>superior mesenteric vein thrombus</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>17</td>
<td>Hematemesis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>18</td>
<td>Hypercoagulation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>20</td>
<td>Diffuse colitis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>20</td>
<td>Pelvic free fluid</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021015</td>
<td>Surgicel</td>
<td>20</td>
<td>Melanic stool</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>
This case concerns a 77 year old female subject who experienced a fatal serious adverse event of pulmonary artery thrombosis. This subject underwent partial hepatectomy with bile duct reconstruction on Study Day 1. The subject was randomized to the comparator treatment for secondary treatment of hemostasis. Post-surgery, the subject presented with oliguria and creatinine values raised to 2.1 (normal range and units were not provided). On Study Day 3, two days after surgery had been performed; the subject became short of breath and was diagnosed with pulmonary artery embolism. Interventional intubation, administration of vasopressors, angio/radiology procedure with right pulmonary artery thrombolysis, intravenous catheter filter and temporary dialysis catheter placement were performed. The subject died due to pulmonary artery embolism and multi organ failure on Study Day 11. The investigator attributed the event pulmonary artery embolism to the subject’s underlying disease of cancer and the recent surgery. The subject's recent surgery represents a compelling alternative etiology, as pulmonary artery embolism is commonly observed post-operatively in immobilized subjects. In addition, the subject’s medical history of transient ischemic attack is suggestive of an latent vascular disease with potential development of an embolism.
### Adverse Events Table

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>3</td>
<td>hypocalcemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>3</td>
<td>tachycardia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>3</td>
<td>Acute Kidney Injury</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>3</td>
<td>pulmonary artery thrombus</td>
<td>FATAL</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>4</td>
<td>hypotension</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>4</td>
<td>Atrial Fibrillation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>4</td>
<td>metabolic acidosis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>4</td>
<td>anemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>5</td>
<td>hypoglycemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>5</td>
<td>enterococcus bacteremia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>6</td>
<td>thrombocytopenia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4015014</td>
<td>Surgicel</td>
<td>8</td>
<td>constipation</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>

**4001043**

73 y.o. male
Hepatic lobectomy with diaphragm repair

**TachoSil**

This case concerns a 73 year old male subject who experienced a fatal serious adverse event of gastrointestinal hemorrhage and a nonfatal serious adverse event of cardiac arrest. This subject underwent surgery with heptectomy, diaphragm repair and test tube placement on [Study Day 1](#). The subject was randomized to TachoSil for secondary surgical hemostasis. Two patches of TachoSil were applied. On Study Day 5, four days after initial surgery, the subject was found unresponsive in the early evening with massive bloody emesis. Pulseless electric activity arrest was detected and resuscitative efforts were initiated. The subject’s pulse was regained and the subject was transferred to the surgical intensive care unit. Packed red blood cells were administered for the massive hematemesis which was probably secondary to
esophageal varices. In the evening on Study Day 5, active massive bleeding was detected in the subject’s esophagus, but visualization of the source of bleeding was not possible. An attempt to place bands blindly was unsuccessful. Massive transfusion protocol was applied. Some hours later, around midnight, asystole was observed, transfusion protocol was stopped and the subject died due to the massive gastrointestinal bleed on Study Day 6.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Hypovolemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Right pneumothorax</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Intermittent sinus tachycardia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Hypertension</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Coagulopathy</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Acute blood loss anemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Bibasilar atelectasis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>Hyperglycemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>1</td>
<td>hepatic cirrhosis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>2</td>
<td>Methicillin-resistant staphylococcus aureus (MRSA)</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>2</td>
<td>Oliguria</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>3</td>
<td>Constipation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>4</td>
<td>Intermittent hiccups</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>4</td>
<td>Hypokalemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>4</td>
<td>Severe epigastric pain</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>4</td>
<td>Post-op ileus</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>
### Adverse Events

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>5</td>
<td>Pulseless Electrical Activity Arrest</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>5</td>
<td>Nausea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>5</td>
<td>Emesis</td>
<td>Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>5</td>
<td>Left pneumothorax</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4001043</td>
<td>TachoSil</td>
<td>5</td>
<td>Massive GI bleed</td>
<td>FATAL</td>
</tr>
</tbody>
</table>

### Narrative

This case concerns a 48 year-old male subject who experienced fatal serious adverse events of acute hepatic failure and cardiorespiratory arrest, and nonfatal serious adverse events of infectious peritonitis and hepatorenal syndrome. This subject underwent right hepatectomy with portal vein, inferior vena cava and bile duct resection and reconstruction on (Study Day 1). The subject was randomized to TachoSil, for secondary treatment of hemostasis. Two and a half patches of TachoSil were applied. On Study Day 4, three days after surgery, acute hepatic failure was diagnosed. White blood count (WBC) had decreased from 12.9 K/UL on Study Day 11 to 5.8 K/UL on Study Day 13. Platelet count had generally been low between 64-53 K/UL from Study Day 10 and 12, and decreased further to 42 K/UL on 28-AUG-2011. On Study Day 13, the subject developed ascites fluid infection with Enterobacter cloacae. No abscess was located. Additionally increased AST and ALT values had been noted in the full period. On Study Day 14, the subject was diagnosed with hepatorenal syndrome. The subject had started therapy with vancomycin, octreotide, fluconazole and piperacillin/tazobactam. On Study Day 27, the subject developed acute ventilatory decompensation leading to cardiopulmonary arrest and death. The investigator considered the events as not related to study treatment, and put forward the underlying disease as alternative etiology and post-operative hepatic failure as the etiology for the hepatorenal syndrome.
### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 3  
**Adverse Event (AE):** Sinus Tachycardia  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 4  
**Adverse Event (AE):** Acute Liver Failure  
**Outcome:** FATAL

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 13  
**Adverse Event (AE):** Ascites Fluid Infection  
**Outcome:** Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 14  
**Adverse Event (AE):** Hepatorenal Syndrome  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 17  
**Adverse Event (AE):** Acute Respiratory Distress  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 18  
**Adverse Event (AE):** Atrial Fibrillation  
**Outcome:** Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 18  
**Adverse Event (AE):** Worsening Anemia  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 19  
**Adverse Event (AE):** Hypothermia  
**Outcome:** Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 19  
**Adverse Event (AE):** Acute Kidney Injury  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 22  
**Adverse Event (AE):** MSSA Pneumonia  
**Outcome:** Not Recovered

### Patient ID 4011005
**Study Arm:** TachoSil  
**AE Onset Study Day:** 27  
**Adverse Event (AE):** Death related to Cardiopulmonary Arrest  
**Outcome:** FATAL

---

This case concerns a 75 year-old male subject who experienced a fatal serious adverse event of multi-organ failure. This subject underwent right hepatectomy, cholecystectomy, left nephrectomy and left adrenalectomy on (b) (6) (Study Day 1). The subject was randomized to TachoSil, for secondary treatment of hemostasis. Five patches were used during surgery. On Study Day 7, the subject
developed multiorgan failure (liver failure, acute respiratory distress syndrome, renal failure). The subject was placed on ventilator and continuous venovenous hemodialysis and sepsis/septic shock protocol was initiated for elevated white blood cell count (white blood cell count reported was 53.6 (no normal range was provided). Interventional therapy with intravenous vancomycin, piperacillin/tazobactam, metronidazole and fluconazole and general life supporting therapy was initiated. No cultures were returned as positive. During the post-operative course the subject’s condition deteriorated and on Study Day 11, the subject died. Autopsy was declined by the subject’s family. Death cause was reported to be multiorgan failure and metastatic colon cancer. The reporting investigator considers the event as not related to study treatment, but due to the subject’s underlying disease of metastatic colon cancer and stress of extensive surgery. Confounding factors in this case is the subject’s medical history of metastatic colon cancer, renal cell carcinoma who underwent right hepatectomy, cholecystectomy, left nephrectomy and left adrenalectomy, the development of multi organ failure with liver failure, acute respiratory distress syndrome, renal failure, is assessed as not related to study treatment but rather to the subject morbidity and postoperative surgical complications.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4011011</td>
<td>TachoSil</td>
<td>1</td>
<td>Liver Steatosis</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4011011</td>
<td>TachoSil</td>
<td>4</td>
<td>Atrial Fibrillation</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4011011</td>
<td>TachoSil</td>
<td>6</td>
<td>cardiogenic shock</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4011011</td>
<td>TachoSil</td>
<td>6</td>
<td>Hyperkalemia</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4011011</td>
<td>TachoSil</td>
<td>7</td>
<td>Multiorgan Failure</td>
<td>FATAL</td>
</tr>
</tbody>
</table>
### Patient ID: 4021020

**Study Arm:** TachoSil

**Adverse Event (AE):** Liver failure

**Outcome:** FATAL

---

**Narrative:** This case concerns a 59 year old male subject who experienced a fatal serious adverse event of hepatic failure and a nonfatal serious adverse event of abdominal infection. This subject underwent liver surgery on [Study Day 1]. The subject was randomized to TachoSil for secondary hemostasis. Three patches were applied during surgery. On Study Day 18, the subject developed liver failure cholestasis. The subject died due to the event liver failure on Study Day 126. No autopsy was performed. The investigator considered the relationship to study treatment as not related but attributed the event to the subject’s underlying liver disease and recent liver lobectomy.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>1</td>
<td>Acute myocardial infarction</td>
<td>FATAL</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>2</td>
<td>Jaundice</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>2</td>
<td>Elevated bilirubin</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>8</td>
<td>Persistent night time agitation</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>11</td>
<td>Biloma</td>
<td>Recovered with Sequelae</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>11</td>
<td>Head laceration</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>11</td>
<td>Intra-abdominal infection</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>13</td>
<td>Fever</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>18</td>
<td>Liver failure</td>
<td>FATAL</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>22</td>
<td>VRE (vancomycin resistant enterococcus)</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>75</td>
<td>Bile leak (x2)</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>110</td>
<td>Fever</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>110</td>
<td>Nausea</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>110</td>
<td>abdominal pain</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>110</td>
<td>intra-abdominal infection</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021020</td>
<td>TachoSil</td>
<td>?</td>
<td>Fibrosis</td>
<td>UNKNOWN</td>
</tr>
</tbody>
</table>
**Study TC-2402-040-SP: Deaths of Pediatric Subjects – Narrative and Serious Adverse Events**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
<th>Narrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>4021021</td>
<td>TachoSil</td>
<td></td>
<td></td>
<td></td>
<td>This case concerns a 6 month-old female subject who experienced a fatal serious adverse event of exsanguinations and nonfatal serious adverse events of disseminated intravascular coagulation, mycobacterium abscessus infection, portal vein thrombosis, hepatic necrosis, enterobacter infection, anastomotic complication, splenic rupture, septic shock, stenotrophomonas infection. The subject underwent liver surgery (Study Day 1). The subject had a medical history of liver transplantation, primary hyperoxaluria, and end stage kidney disease. The subject was randomized to TachoSil for secondary hemostasis. One patch of TachoSil was applied during surgery. On Study Day 12, the subject developed disseminated intravascular coagulopathy and a positive blood culture revealed Mycobacterium abscessus. The outcome of both of these events is unknown. The investigator considered the relationship to study drug as not related but provided alternative etiology as Mycobacterium abscessus. On Study Day 13, the subject developed liver failure. A portal vein thrombosis was diagnosed on Study Day 13 and a thrombectomy and liver biopsy was performed (artery flow was found normal) the same day. The liver biopsy revealed markedly increased amount of ischemia-induced hepatocytes necrosis. No portal inflammation, no bile duct damage, and no venulitis nor fibrosis was identified. The event of portal vein thrombosis and hepatic necrosis resolved on Study Day 13 and 16, respectively. The investigator considered the relationship to study drug as not related but attributed the event to the subject’s status...</td>
</tr>
</tbody>
</table>
A second transplant was performed on Study Day 15. Due to failure of the graft following the second transplantation, the subject underwent repeated surgeries (washouts and explorative laparotomies). On Study Day 22, the subject was found to have a perforation of the previous Roux-en-Y anastomosis, splenic rupture in addition to necrotic liver. The subject had suffered from significant blood loss and was transferred to the pediatric intensive care unit where vasopressor treatment was initiated. Repeated washouts and in addition, a resection of the infarcted portion of the transplanted liver was performed. The subject’s liver function declined further during the course of hospitalization. The subject developed profound septic shock and an infection with stenotrophomonas maltophilia and enterobacter cloacae on Study Day 29 as well as profound metabolic acidosis, lactic acidosis, thrombocytopenia, anemia and displayed signs of disseminated intravascular coagulopathy. The subject died due to exsanguination secondary to disseminated intravascular coagulopathy in the setting of septic shock on Study Day 43. None of the events of mycobacterium abscessus infection, enterobacter infection, anastomotic complication, splenic rupture, septic shock, and stenotrophomonas infection recovered before the subject’s death.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Study Arm</th>
<th>AE Onset Study Day</th>
<th>Adverse Event (AE)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4021021</td>
<td>TachoSil</td>
<td>2</td>
<td>Gastrointestinal anastomotic leak/Roux-en-Y leak</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021021</td>
<td>TachoSil</td>
<td>12</td>
<td>Disseminated intravascular coagulopathy</td>
<td>Not Recovered</td>
</tr>
<tr>
<td>4021021</td>
<td>TachoSil</td>
<td>13</td>
<td>Portal vein thrombosis</td>
<td>Recovered</td>
</tr>
<tr>
<td>4021021</td>
<td>TachoSil</td>
<td>22</td>
<td>Anastomotic complication/perforated roux en-y anastomosis</td>
<td>Not Recovered</td>
</tr>
</tbody>
</table>
6.1.12.4 Nonfatal Serious Adverse Events

The following table shows the frequency of adverse events by body system in adults:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>21</td>
<td>18</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>25</td>
<td>21</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>12</td>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Investigations</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Social circumstances</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reviewer comment:** Comparable numbers of adult subjects in both treatment arms experienced adverse events in all body system categories.

The following table shows the frequency of adverse events by body system in pediatric subjects:

<table>
<thead>
<tr>
<th>Study Study TC-2402-040-SP: Serious Adverse Events in Pediatric Subjects</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
</table>
as an adjunct to hemostasis for adult and pediatric hepatic resection surgery
Clinical Review Memo – Charles Maplethorpe, MD., Ph.D. CBER/OBRR/DHCR/HPRB

<table>
<thead>
<tr>
<th>Body System</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The body system category “Gastrointestinal disorders” for the pediatric subjects is shown in the following table by seriousness and treatment group:

**Study Study TC-2402-040-SP: Serious and Non-serious Adverse Events in Pediatric Subjects for the Body System Category “Gastrointestinal disorders”**

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Reported Adverse Event Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>Diarrhea</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>Abdominal Pain</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>Acute Vomiting</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>GI Bleed</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>Fluid Collection At Cut Surface of The Liver</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Constipation</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Emesis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Non-serious</td>
<td>Ascites</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Bloody Stools</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Chylous Ascites</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Diarrhea</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Distended Abdomen</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Esophageal Ulcer</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Gas</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-serious</td>
<td>Hyperactive Bowel Sounds</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>Loose Stools</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
6.12.5 Adverse Events of Special Interest (AESI)

FDA requested monitoring of study TC-2402-040-SP for antibody formation against equine collagen and against human fibrinogen, based on earlier observations of antibody formation.

The following table summarizes the results of antibody monitoring:
### Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Antigen</th>
<th>Visit</th>
<th>Date/Day of Sample</th>
<th>Sample Status</th>
<th>Immunogenicity Result</th>
<th>Cross-Reactivity Titer</th>
<th>Visit</th>
<th>Date/Day of Sample</th>
<th>Sample Status</th>
<th>Immunogenicity Result</th>
<th>Cross-Reactivity Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>US4001027</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>21 October 2011/1</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-Month follow-up</td>
<td>09 November 2011/20</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-Month follow-up</td>
<td>08 February 2012/111</td>
<td>Normal</td>
<td>Positive</td>
<td>188</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-Month follow-up</td>
<td>18 March 2014/880</td>
<td>Normal</td>
<td>Positive</td>
<td>159</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td>US4007008</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>28 February 2011/1</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-Month follow-up</td>
<td>31 March 2011/32</td>
<td>Normal</td>
<td>Positive</td>
<td>806</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-Month follow-up</td>
<td>27 May 2011/89</td>
<td>Normal</td>
<td>Positive</td>
<td>904</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-Month follow-up</td>
<td>27 May 2014/1185</td>
<td>Normal</td>
<td>Positive</td>
<td>159</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td>US4007019</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>05 March 2012/1</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-Month follow-up</td>
<td>03 April 2012/30</td>
<td>Normal</td>
<td>Positive</td>
<td>440</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-Month follow-up</td>
<td>01 June 2012/89</td>
<td>Normal</td>
<td>Positive</td>
<td>1480</td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>
### Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Antigen</th>
<th>Visit</th>
<th>Date/Day of Sample</th>
<th>Sample Status</th>
<th>Immunogenicity</th>
<th>Cross-Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eqCollagen</td>
<td>24-Month follow-up (long-term)</td>
<td>23 April 2014/780</td>
<td>Normal</td>
<td>Positive</td>
<td>222</td>
</tr>
<tr>
<td>US4010003</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>14 March 2011/1</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eqCollagen</td>
<td>1-Month follow-up</td>
<td>28 April 2011/46</td>
<td>Normal</td>
<td>Positive</td>
<td>702</td>
</tr>
<tr>
<td></td>
<td>eqCollagen</td>
<td>24-Month follow-up (long-term)</td>
<td>15 April 2014/1129</td>
<td>Normal</td>
<td>Positive</td>
<td>53</td>
</tr>
<tr>
<td>US4012001</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>21 April 2011/1</td>
<td>Normal</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eqCollagen</td>
<td>1-Month follow-up</td>
<td>25 May 2011/35</td>
<td>Other: coordinator unable to properly assess</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eqCollagen</td>
<td>3-Month follow-up</td>
<td>29 July 2011/100</td>
<td>Other: coordinator unable to properly assess</td>
<td>Positive</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>eqCollagen</td>
<td>24-Month follow-up (long-term)</td>
<td>02 June 2014/1139</td>
<td>Positive</td>
<td>116</td>
<td>Negative</td>
</tr>
</tbody>
</table>
### Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Antigen</th>
<th>Visit</th>
<th>Date/Day of Sample</th>
<th>Sample Status</th>
<th>Immunogenicity Result</th>
<th>Cross-Reactivity Result</th>
<th>Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>US4018013</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>26 July 2011/1</td>
<td>Other: Not specified</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-Month follow-up</td>
<td>24 August 2011/30</td>
<td>Other: Not specified</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-Month follow-up</td>
<td>02 November 2011/100</td>
<td>Other: Not specified</td>
<td>Positive</td>
<td>576</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-Month follow-up</td>
<td>18 June 2014/1059</td>
<td>Other: Not specified</td>
<td>Positive</td>
<td>1279</td>
<td></td>
</tr>
<tr>
<td>US4018016</td>
<td>eqCollagen</td>
<td>Baseline</td>
<td>27 September 2011/1</td>
<td>Other: Not specified</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-Month follow-up</td>
<td>19 October 2011/23</td>
<td>Other: Not specified</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-Month follow-up</td>
<td>04 January 2012/100</td>
<td>Other: Not specified</td>
<td>Positive</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-Month follow-up</td>
<td>18 June 2014/996</td>
<td>Other: Not specified</td>
<td>Positive</td>
<td>463</td>
<td></td>
</tr>
</tbody>
</table>

Day is relative to the day of surgery (Day 1).

Note: Cross-reactivity testing was only performed when the serum sample tested positive for equine collagen antibodies.
Reviewer comment: 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.

6.1.12.7 Dropouts and/or Discontinuations

From STN125351/172 clinical report page 94 of 186:

- A total of 26 patients (15 patients in the TachoSil group and 11 patients in the Surgicel Original group) were excluded from the PP based on events that occurred on the day of surgery.
  - The most common reason for exclusion from the PP was “randomized prior to primary hemostatic measures” (12 patients in the TachoSil group and 11 patients in the Surgicel Original group).
  - Two patients (Patients 4004001 and 4012006) in the Surgicel Original group who were excluded from the PP due to the reason of “randomized prior to primary hemostatic measures” also had other deviations that led to exclusion:
    - “radiofrequency pre-coagulation of the liver resection wound except focal radiofrequency ablation of vessels as primary hemostatic treatment” (Patient 4004001) and
    - “expected ability to lightly press the trial treatment to the liver resection wound for 3 minutes”, “minor to moderate bleeding from the resection area persisting after conventional resection procedure and primary control of arterial pulsating bleeding or major venous hemorrhage”, and “need for additional supportive hemostatic treatment” (Patient 4012006).
  - Other reasons for exclusion from the PP included:
    - “Time to hemostasis <8 minutes and 2nd treatment application recorded”. This was recorded for 2 patients in the TachoSil group (Patients 4016003 and 4021013). Patients who achieved hemostasis at 5 minutes or earlier but received a second treatment application were violating the treatment regimen and were therefore excluded from the PP (note that, after the 5-minute time point, the next time point for checking hemostasis was 8 minutes).
    - “Patient's age is invalid for the randomization schedule used”. This was recorded for 1 patient in the TachoSil group (Patient 4007014) who was allocated to the wrong age group due to an error in
entering the birth date in the IVRS. The patient was 64 years old and should therefore have been allocated to the adult group; however, he was allocated to the 0 to 23 months age group because the screening date was incorrectly entered as the date of birth.

- A total of 3 pediatric patients (1 patient in the TachoSil group and 2 patients in the Surgicel Original group) had protocol deviations recorded in Listing 26.2.2.1.1 (in the submission):
  - 1 patient in the TachoSil group (Patient 4021005) was randomized prior to primary hemostatic measures
  - 1 patient in the Surgicel Original group (Patient 4021014) received a hemostatic treatment other than the trial treatment between randomization and the time to hemostasis (or 10-minute evaluation), and had rescue medication applied less than 10 minutes after trial treatment application
  - 1 patient in the Surgicel Original group (Patient 4022004) had missing baseline immunogenicity data

- No patients in the pediatric FAS group had actual treatment differing from randomized treatment (Appendix 16.2, Listing 26.2.2.1.3 in the submission).

**Reviewer’s Comment:** The dropout rate and reasons for dropout are acceptable.

6.1.13 Study Summary and Conclusions

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 patients.

9. ADDITIONAL CLINICAL ISSUES

9.1.3 Pediatric Use and PREA Considerations

The April 5, 2010, approval letter for TachoSil contained the following statement regarding the PREA requirement:

```
We are deferring submission of your pediatric study until December 2010 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section
```
TachoSil (Fibrin Sealant Patch) (Takeda Pharma A/S)
as an adjunct to hemostasis for adult and pediatric hepatic resection surgery
Clinical Review Memo – Charles Maplethorpe, MD., Ph.D. CBER/OBRR/DHCR/HPRB

505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for use of TachoSil as an adjunct to hemostasis in pediatric patients 0-16 years undergoing hepatic resection surgery.

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 (see below). 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.

10. CONCLUSIONS

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

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>• Liver surgery creates large areas of parenchymal bleeding that must be addressed before surgical closure.</td>
<td>• TachoSil has demonstrated safety and efficacy for use as an adjunct to hemostasis in liver surgery.</td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td>• There are several fibrin sealant products available for use as an adjunct to hemostasis</td>
<td>• There is no unmet medical need because the clinical studies have not demonstrated a more</td>
</tr>
<tr>
<td>Decision Factor</td>
<td>Evidence and Uncertainties</td>
<td>Conclusions and Reasons</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td>in various surgical settings.</td>
<td>significant clinical benefit from the use of TachoSil compared to that of other adjunct to hemostasis products.</td>
</tr>
</tbody>
</table>

**Clinical Benefit**

- The indication for use as an adjunct to hemostasis in adult liver surgery is supported by the results of clinical study TC-2402-040-SP (TachoSil: 114 adults, 20 pediatric subjects; control Surgicel: 110 adults, 9 pediatric subjects)
  - Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure.
  - Perhaps the major benefit from the licensure of these products has been the decreased use of the surgical practice of “home brew” fibrin
- TachoSil has demonstrated clinical benefit for use as an adjunct to hemostasis in adult liver surgery, according to the surrogate endpoint percent of subjects achieving hemostasis at 3 minutes.
<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
</table>
| Risk           | - TachoSil contains human thrombin and human fibrinogen on an equine collagen patch, and therefore, there is a theoretical risk for perturbation of the coagulation system.  
- The absorbable matrix pad delivery system is novel, and therefore, potential effects on immunogenicity have not been fully evaluated. Fifty percent of subjects form antibodies to equine collagen, however, these antibodies do not cross-react on human collage, and no immune-related adverse events have been observed. | - All the evidence indicates that the risk associated with the use of TachoSil as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity. Immune-related clinical problems have not been observed. |
| Risk Management | - Potential for perturbation of the coagulation system (e.g. thrombogenicity) | - Routine pharmacovigilance should address the concern for potential perturbation of the coagulation system. |
### Decision Factor

<table>
<thead>
<tr>
<th>Evidence and Uncertainties</th>
</tr>
</thead>
</table>

### Conclusions and Reasons

- Routine pharmacovigilance should address the concern for potential for adverse events because of possibly increased immunogenicity.

  Immunogenicity monitoring of the hepatic surgery study TC-2402-040-SP has alleviated immediate concerns about immunogenicity.

- Potential for adverse events because of possibly increased immunogenicity.

### 11.2 Risk-Benefit Summary and Assessment

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

### 11.4 Recommendations on Regulatory Actions
The sought indication in STN 125351/172, for use with manual compression in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical can be approve. There should be a limitation of use excluding neonates (less than 30 days of age) because this group was not studied.

11.5 Labeling Review and Recommendations

There were no disagreements with the applicant over changes to the submitted labeling recommended by FDA. The attached package insert can be approved.

11.6 Recommendations on Postmarketing Actions.

There are no recommended post-marketing requirements or commitments for clinical purposes. Routine post-marketing surveillance is recommended.
# Appendix 1. Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post-procedural bile leak</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Dehydration</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Localised intraabdominal fluid collection</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Abdominal abscess</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Postoperative wound infection</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Atrial fibrillation</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Impaired gastric emptying</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Infectious peritonitis</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Liver abscess</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Wound infection</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Hepatic neoplasm malignant recurrent</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to liver</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to lung</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary embolism</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Leukocytosis</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Bundle branch block right</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Cardiac arrest</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Cardio-respiratory arrest</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Congenital, familial and genetic disorders</td>
<td>Syringomyelia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Endocrine disorders</td>
<td>Goitre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain upper</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Ascites</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Colitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal haemorrhage</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Gastrooesophageal reflux disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Intestinal perforation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Oesophagitis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Multi-organ failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Non-cardiac chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Acute hepatic failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Bile duct obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Biloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hepatorenal syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Abdominal infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Bacteraemia</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Clostridial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Clostridium difficile colitis</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Escherichia sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Haematoma infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 109</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 114</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Lobar pneumonia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Subdiaphragmatic abscess</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Viral infection</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Postoperative adhesion</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Seroma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Fluid overload</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypophagia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to peritoneum</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Psychiatric disorders</td>
<td>Confusional state</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Psychiatric disorders</td>
<td>Delirium</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Psychiatric disorders</td>
<td>Mental status changes</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Renal and urinary disorders</td>
<td>Renal failure acute</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Renal and urinary disorders</td>
<td>Urethral haemorrhage</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Aspiration</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pleural effusion</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pneumothorax</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary oedema</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory failure</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Social circumstances</td>
<td>Activities of daily living impaired</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Iron deficiency anaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Cardiac tamponade</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Pericarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Cardiac disorders</td>
<td>Supraventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Enterocutaneous fistula</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Ileal fistula</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Ileus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Small intestinal obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Small intestinal perforation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Device occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Hernia obstructive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Bile duct stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Cholangitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic ischaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hyperbilirubinaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Jaundice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Portal vein thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Appendicitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Bacterial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Enterococcal bacteraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Klebsiella infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Peritoneal abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Postoperative abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix A: Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Sepsis</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Staphylococcal infection</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Urosepsis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Wound abscess</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Wound infection staphylococcal</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural haemorrhage</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Vascular graft thrombosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Investigations</td>
<td>Antibiotic resistant Staphylococcus test positive</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Investigations</td>
<td>False positive investigation result</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Failure to thrive</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemic hyperosmolar nonketotic syndrome</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Colorectal cancer recurrent</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Hepatic cancer metastatic</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to bone</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to lymph nodes</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Nervous system disorders</td>
<td>Cerebral infarction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Nervous system disorders</td>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Renal and urinary disorders</td>
<td>Renal failure</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinial disorders</td>
<td>Dyspnoea</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinial disorders</td>
<td>Pneumonia aspiration</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Respiratory, thoracic and mediastinial disorders</td>
<td>Pulmonary artery thrombosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Vascular disorders</td>
<td>Deep vein thrombosis</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Vascular disorders</td>
<td>Shock</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Vascular disorders</td>
<td>Thrombophlebitis superficial</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Atelectasis</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypophosphataemia</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site</td>
<td>Pyrexia</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pleural effusion</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site</td>
<td>Oedema peripheral</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalaemia</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Ascites</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypomagnesaemia</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Oliguria</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal distension</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
### APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Urinary retention</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Leukocytosis</td>
<td>11</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>15</td>
<td>13</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Sinus tachycardia</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Fluid overload</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Confusional state</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural bile leak</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypocalcaemia</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hypoxia</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic steatosis</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Dehydration</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperkalaemia</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypovolaemia</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal failure acute</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pneumothorax</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Localised intraabdominal fluid collection</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
## Appendix  Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Asthenia</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site pain</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Breath sounds abnormal</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>International normalised ratio increased</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Transaminases increased</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Urine output decreased</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypoalbuminaemia</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Agitation</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Hallucination</td>
<td></td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hiccups</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Oropharyngeal pain</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary oedema</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Haemorrhagic anaemia</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Atrial fibrillation</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal hernia</td>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain upper</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Flatulence</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Chills</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Jaundice</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Enterococcal infection</td>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Staphylococcal infection</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Wound infection</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
## APPENDIX  ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Open wound</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Postoperative ileus</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural pain</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Wound dehiscence</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperphosphataemia</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal chest pain</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Delirium</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Mental status changes</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Benign prostatic hyperplasia</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bradypnoea</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory failure</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Rhinorrhoea</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Wheezing</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Leukopenia</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Sinus bradycardia</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal discomfort</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Faecaloma</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastrooesophageal reflux disease</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Ileus</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site</td>
<td>Granuloma</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Temperature intolerance</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Biloma</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Bronchitis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Clostridial infection</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Clostridium difficile colitis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Incision site cellulitis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Pneumonia</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Excoriation</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Fall</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Hepatic haematoma</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incisional hernia</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Suture related complication</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood bilirubin increased</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Chest X-ray abnormal</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Heart rate decreased</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Liver function test abnormal</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Respiratory rate increased</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Weight decreased</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Hepatic neoplasm</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Paraesthesia</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Dysuria</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Haematuria</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Incontinence</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal impairment</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Pelvic pain</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Acute respiratory distress syndrome</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Night sweats</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Coagulopathy</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Hypocoagulable state</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Iron deficiency anaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Splenic infarction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Splenic vein thrombosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Bradycardia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Bundle branch block left</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Cardiogenic shock</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Cardiomegaly</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Cardiopulmonary failure</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Left ventricular dysfunction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Mitral valve calcification</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix  Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Pericardial effusion</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Supraventricular extrasystoles</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Ventricular extrasystoles</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Ear and labyrinth disorders</td>
<td>Deafness</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Ear and labyrinth disorders</td>
<td>Ear pain</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Visual impairment</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal tenderness</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Anorectal discomfort</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Crohn's disease</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Dysphagia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastric disorder</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal sounds abnormal</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Haemorrhoids</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Hiatus hernia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Intestinal dilatation</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Intra-abdominal haemorrhage</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Lip blister</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Mesenteric vein thrombosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Oesophagitis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Pneumoperitoneum</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Stomatitis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site</td>
<td>Catheter site pain</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness Conditions</th>
<th>Body System Conditions</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Device leakage</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Fat necrosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Generalised oedema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Hypothermia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Implant site effusion</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Localised oedema</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Medical device complication</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Mucosal inflammation</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Secretion discharge</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Biliary fistula</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic cirrhosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic cyst</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic fibrosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic ischaemia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic lesion</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hyperbilirubinaemia</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Portal vein thrombosis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Abdominal infection</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Abdominal sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Bacteraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Bacteroides bacteraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Cellulitis</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Escherichia infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Fungal infection</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Localised infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Oral infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Pneumonia staphylococcal</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Postoperative abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Postoperative wound infection</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Sepsis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Sinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Skin infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Tooth abscess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Tracheobronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Urinary tract infection bacterial</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Corneal abrasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Endotracheal intubation complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Fibula fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site complication</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site pruritus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Laceration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Page 77
### APPENDIX: ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Postoperative fever</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural haemorrhage</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural hypertension</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural hypotension</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural nausea</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Seroma</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Wound</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Wound secretion</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Alpha 1 foetoprotein increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood creatinine decreased</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood creatinine increased</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood lactic acid increased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood urea increased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Body temperature decreased</td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Body temperature increased</td>
<td>3</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Coagulation time prolonged</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Haematocrit decreased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Hepatic enzyme increased</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Lipase increased</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Mean arterial pressure decreased</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Prothrombin time prolonged</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Respiratory rate decreased</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Total lung capacity decreased</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Troponin increased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Weight increased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Appendix Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Investigations</td>
<td>White blood cell count increased</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Acidosis</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Cachexia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Diabetes mellitus</td>
<td></td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Failure to thrive</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Lactic acidosis</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Malnutrition</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Vitamin B1 deficiency</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Mobility decreased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Basal cell carcinoma</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Colon adenoma</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Colorectal cancer metastatic</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Lung neoplasm</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to adrenals</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to bone</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Peritoneal neoplasm</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Recurrent cancer</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Hypoesthesia</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Lethargy</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Neuropathy peripheral</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Restless legs syndrome</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Sciatica</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Sedation</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Tremor</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Mental disorder</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Panic attack</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Anuria</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Neurogenic bladder</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Pyuria</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Dysmenorrhoea</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Penile oedema</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Aspiration</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Asthma</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dry throat</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dysphonia</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea exertional</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Haemoptysis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hydropneumothorax</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hypoventilation</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Orthopnoea</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary congestion</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary embolism</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary hypertension</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory acidosis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory depression</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Rhonchi</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Tachypnoea</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Blister</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermal cyst</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis contact</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dry skin</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hyperhidrosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Intertrigo</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Palmar-plantar erythrodysaesthesia syndrome</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Petechiae</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>10</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash generalised</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash papular</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin disorder</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin fissures</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin irritation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin lesion</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Surgical and medical procedures</td>
<td>Incisional drainage</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 109</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 114</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>N</td>
<td>Surgical and medical procedures</td>
<td>Wound drainage</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Vascular calcification</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Heparin-induced thrombocytopenia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Hypercoagulation</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Lymphadenopathy</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Neutrophilia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Diastolic dysfunction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Pericardial haemorrhage</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Endocrine disorders</td>
<td>Hypothyroidism</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Endocrine disorders</td>
<td>Thyroid disorder</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Conjunctivitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Dry eye</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Lacrimation increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Ocular icterus</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Colitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Colonic polyp</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Faeces pale</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastric dilatation</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastritis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disorder</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gingival pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Haematemesis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Haematochezia</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Impaired gastric emptying</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Inguinal hernia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Intestinal mucosal hypertrophy</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Lip dry</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Malabsorption</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Melaena</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Mesenteric occlusion</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Oesophageal ulcer</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Oral pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Peritoneal disorder</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Retroperitoneal oedema</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Small intestinal obstruction</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Chest discomfort</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Chest pain</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Impaired healing</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Influenza like illness</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Infusion site swelling</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Malaise</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Non-cardiac chest pain</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Oedema</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Bile duct stenosis</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 109</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 114</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Dilatation intrahepatic duct acquired</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic infarction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Periportal oedema</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Portal vein occlusion</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Bacterascites</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Candidiasis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Catheter site infection</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Clostridium colitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Cystitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Device related infection</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Diverticulitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Enterococcal bacteraemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Fungaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Fungal skin infection</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Implant site pustules</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Infectious peritonitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Intertigo candida</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Liver abscess</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Perihepatic abscess</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Pharyngitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Anaemia postoperative</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Arteriovenous fistula site complication</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Head injury</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site erythema</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site haemorrhage</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site oedema</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural haemorrhage</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Postoperative wound complication</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Toxicity to various agents</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Urinary retention postoperative</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Vascular procedure complication</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Ammonia increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Antibiotic resistant Staphylococcus test positive</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood albumin decreased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood alkaline phosphatase increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood magnesium decreased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood pressure increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Carbohydrate antigen 19-9 increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Cardiac enzymes increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Neutrophil count increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Oxygen consumption increased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Spinal X-ray abnormal</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Electrolyte imbalance</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Gout</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypoproteinaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Metabolic acidosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Flank pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Hypercreatinemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Neck pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 109</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 114</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rhabdomyolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Metastases to retroperitoneum</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Rectal cancer metastatic</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Tumour invasion</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Encephalopathy</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Memory impairment</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Mental impairment</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Nerve compression</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Sensory loss</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Sinus headache</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Toxic neuropathy</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Disorientation</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Pollakiuria</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Polyuria</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Proteinuria</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal cyst</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal failure</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal tubular necrosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Urinary hesitation</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Urine flow decreased</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Dyspareunia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 109</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 114</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------</td>
<td>----------------------------</td>
<td>----------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Pelvic fluid collection</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Prostatitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Scrotal swelling</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Uterine mass</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Acute respiratory failure</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Allergic respiratory symptom</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Apnoea</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchial secretion retention</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hypercapnia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hyperoxia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Increased viscosity of bronchial secretion</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Painful respiration</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Productive cough</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Rales</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory distress</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Ecchymosis</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Lichen planus</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Purpura</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash erythematous</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin exfoliation</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Social circumstances</td>
<td>Treatment noncompliance</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Surgical and medical procedures</td>
<td>Colostomy closure</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Bloody discharge</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 1. Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 109</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Haemodynamic instability</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Hypovolaemic shock</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Thrombophlebitis superficial</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Vena cava thrombosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Appendix 2. Pediatric Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Clostridium difficile colitis</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Disseminated intravascular coagulation</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Congenital, familial and genetic disorders</td>
<td>Hydrocele</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal haemorrhage</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>General disorders and administration site conditions</td>
<td>Catheter site swelling</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX  ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Cholangitis</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic artery thrombosis</td>
<td></td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic necrosis</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Hepatobiliary disorders</td>
<td>Portal vein thrombosis</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Alpha haemolytic streptococcal infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Enterobacter infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Enterococcal infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Klebsiella infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Mycobacterium abscessus infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Septic shock</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Stenotrophomonas infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Viraemia</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Anastomotic complication</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Incision site haematoma</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural bile leak</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Injury, poisoning and procedural complications</td>
<td>Splenic rupture</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypophagia</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Vascular disorders</td>
<td>Exsanguination</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Gastrointestinal disorders</td>
<td>Localised intraabdominal fluid collection</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Gastroenteritis</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Infections and infestations</td>
<td>Pneumonia klebsiella</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>Nervous system disorders</td>
<td>Convulsion</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Seriousness</td>
<td>Body System</td>
<td>Adverse Event Decoded Term</td>
<td>Surgicel Events</td>
<td>Surgicel Subjects N = 9</td>
<td>TachoSil Events</td>
<td>TachoSil Subjects N = 20</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Ascites</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Human herpesvirus 6 infection</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Transaminases increased</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypomagnesaemia</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pleural effusion</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Tachypnoea</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Cardiac disorders</td>
<td>Ventricular extrasystoles</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Eye disorders</td>
<td>Eyelid ptosis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal distension</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain lower</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Flatulence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal sounds abnormal</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Haematochezia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Localised intraabdominal fluid collection</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Mallory-Weiss syndrome</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Oesophageal ulcer</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Catheter site haematoma</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Appendix: Adult Adverse Events by Seriousness and Decreasing Frequency by Number of TachoSil Subjects

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Oedema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Oedema peripheral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Hepatic vein stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Portal vein stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Hepatobiliary disorders</td>
<td>Venoocclusive liver disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Immune system disorders</td>
<td>Drug hypersensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Immune system disorders</td>
<td>Liver transplant rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Immune system disorders</td>
<td>Transplant rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Clostridial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Epstein-Barr viraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Parainfluenzae virus infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Peritonitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Pharyngitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Accidental overdose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Gastrointestinal anastomotic leak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Inadequate analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Lower limb fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural bile leak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Toxicity to various agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood glucose decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Blood potassium decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Coagulation time prolonged</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>International normalised ratio increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX  ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Lipase increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>Urine output decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Investigations</td>
<td>White blood cell count increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Acidosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Fluid imbalance</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypophagia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypophosphataemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Iron deficiency</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Metabolic acidosis</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Vitamin D deficiency</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Neck pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Emotional distress</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Emotional poverty</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Suicidal ideation</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Dysuria</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Renal failure acute</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Scrotal swelling</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Atelectasis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### APPENDIX  ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Body System</th>
<th>Adverse Event Decoded Term</th>
<th>Surgicel Events</th>
<th>Surgicel Subjects N = 9</th>
<th>TachoSil Events</th>
<th>TachoSil Subjects N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hypercapnia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pneumothorax</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory distress</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Wheezing</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis diaper</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin disorder</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Blood and lymphatic system disorders</td>
<td>Leukocytosis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Gastrointestinal disorders</td>
<td>Abdominal discomfort</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>General disorders and administration site conditions</td>
<td>Generalised oedema</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Device related infection</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Infections and infestations</td>
<td>Febrile infection</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Hepatic haematoma</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Injury, poisoning and procedural complications</td>
<td>Procedural hypertension</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Dehydration</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Psychiatric disorders</td>
<td>Restlessness</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Renal and urinary disorders</td>
<td>Ketonuria</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Reproductive system and breast disorders</td>
<td>Menorrhagia</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>Vascular disorders</td>
<td>Vena cava thrombosis</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>