



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 January 2015
EMA/18660/2015
Committee for Medicinal Products for Human Use (CHMP)

Tachosil

(Human fibrinogen / Human thrombin)

EMA/H/C/000505/P46 039

CHMP assessment report for paediatric use studies
submitted according to Article 46 of the Regulation (EC)
No 1901/2006

**Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted**



Administrative information

Invented name of the medicinal product:	TachoSil
INN (or common name) of the active substance(s):	(Human fibrinogen / Human thrombin)
MAH:	Takeda Austria GmbH
Currently approved Indication(s)	TachoSil is indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient.
Pharmaco-therapeutic group (ATC Code):	Local haemostatics, ATC code: B02BC30
Pharmaceutical form(s) and strength(s):	Medicated sponge Package with 1 sponge of 9.5 cm x 4.8 cm Package with 2 sponges of 4.8 cm x 4.8 cm Package with 1 sponge of 3.0 cm x 2.5 cm Package with 5 sponges of 3.0 cm x 2.5 cm
Rapporteur's contact person:	Name Maren Hammann Tel: ++49 6103 77 2550 Email: Maren.Hammann@pei.de
Name of the Assessor:	Name Juliane Bitsch Email: Juliane.Bitsch@pei.de
Product PTL:	Name: Kyriaki Tzogani Email: Kyriaki.Tzogani@ema.europa.eu

1. Introduction

On 27 February 2014, the MAH submitted a completed paediatric study(ies) for TachoSil, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Clinical Trial report of study interventional 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.

2. Scientific discussion

2.1. Information on the development program

The clinical trial report was submitted by the MAH as a single application.

2.2. Information on the pharmaceutical formulation used in the study

TachoSil is a sterile ready-to-use absorbable patch for intraoperative topical application. It consists of an equine collagen patch coated with the fibrin glue components: human fibrinogen and human thrombin. The active side is coloured yellow with riboflavin. The product was manufactured by Takeda according to GMP and local national regulations. The patch size was 9.5 cm × 4.8 cm × 0.5 cm (3.7 in × 1.9 in × 0.2 in).

2.3. Clinical aspects

2.3.1. Introduction

Advances in surgical technique have reduced the occurrence of postoperative complications following liver resection, but the management of the raw surface after parenchymal transection may still cause local complications such as bleeding, bile leakage or liver necrosis (Holt et al 2000, Imamura et al 2003). The tendency of the liver to bleed diffusely during surgery is related to its extensive vascularization and the fact that the hepatic sinusoidal structure is not capable of smooth muscle contraction to secure vasoconstriction (Chapman et al 2000). Both morbidity and mortality after liver resection is closely related to intraoperative blood loss. Therefore, the intraoperative control of haemorrhage from the parenchymal resection wound of the liver is still a challenge for the treating surgeon.

TachoSil® is a ready-to-use degradable surgical patch developed for topical use to support intraoperative haemostasis and tissue sealing. The patch consists of a dry foamed collagen carrier of equine origin, coated with human fibrinogen and human thrombin. This fixed combination is intended to be applied directly to the wound surface. TachoSil® was approved by the European Commission in 2004. Later applications for variation to the marketing authorization led to the current European indication issued in 2009 for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. TachoSil® is not indicated for treatment of children <18 years.

Since the approval of TachoSil® in the EU, an estimated number of 2,940,000 patients have been exposed to TachoSil® until 08 June 2012 under the assumption of an average use of 1 patch for each surgical procedure. In the same period, a total of 180 spontaneously reported adverse drug reactions have been reported in 121 patients. A total of 144 adverse drug reactions were considered to be

serious for 95 patients and 36 were non-serious in 26 patients. A total of 133 of the 145 serious adverse drug reactions were unlisted.

Paediatric experience

In the European Union (EU), one clinical trial on the use of TachoSil® in 16 children undergoing liver resection had been conducted already.

2.3.2. Clinical study

Clinical 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.”

Description

The trial was designed to evaluate the clinical efficacy and safety of TachoSil® versus Surgicel® Original, a standard US-licensed haemostatic agent consisting of oxidised regenerated cellulose, in adult and paediatric patients.

Methods

Objective(s)

The primary objective was to show that TachoSil® was superior to Surgicel® Original as secondary haemostatic treatment after hepatic resection surgery and primary haemostatic treatment in adult patients.

Secondary objectives were to evaluate the safety of TachoSil® as secondary haemostatic treatment in hepatic resection surgery and to explore the efficacy and safety of TachoSil® as secondary haemostatic treatment in hepatic resection surgery in paediatric patients.

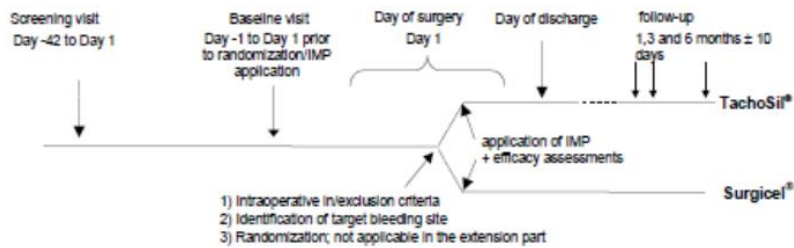
Study design

The study was conducted as a randomised, open-label, controlled, multi-centre trial in adult and paediatric patients.

Randomisation to TachoSil® or Surgicel® Original was conducted during surgery, after completion of primary haemostatic treatment.

Figure 1 depicts trial design according to the trial timeline.

Figure 1: Trial Design



Study population / Sample size

224 patients aged 17 years or older were randomly assigned to trial treatment, 114 patients were allocated to TachoSil® and 110 patients to Surgicel® Original.

Furthermore, 29 paediatric patients aged until 16 years (inclusive) were enrolled. Of these, 17 were randomly assigned to treatment (8 to TachoSil® and 9 to Surgicel®), whereas 12 were enrolled in the context of an extension trial and exclusively treated with TachoSil®, so that in total 20 paediatric patients were treated with TachoSil®.

Assessor's comment:

Within this clinical study, a paediatric part was conducted and analysed separately.

As laid down in Regulation (EC) No. 1906/2006 on medicinal products for paediatric use, the paediatric population is to be defined as that part of the population aged between birth and 18 years. In this study, by contrast, only patients until the age of 16 were included in the paediatric part. But since - according to enclosed demographic data listings - none of the adult trial patients was younger than 18 years, no additional data analysis regarding the paediatric population is necessary.

Main Inclusion Criteria

- Resection of at least the equivalent tissue volume of 1 anatomical segment of the liver for any reason, either by laparotomy or by hand-assisted laparoscopy.
- Minor to moderate (oozing/diffuse) bleeding from the resection area persisting after conventional resection procedure and primary control of arterial pulsating bleeding or major venous haemorrhage by sutures, ligations, clips, vascular stapler, point electrocautery, or focal radiofrequency ablation
- Need for additional supportive haemostatic treatment

Main Exclusion Criteria

- Indication for emergency surgery
- Known coagulopathy (as judged relevant by the Investigator)

- Known or suspected hypersensitivity to any ingredient of the trial treatments (eg, human fibrinogen, human thrombin and/or collagen of any origin)
- Dry surgical field of the targeted application area
- Occurrence of any serious surgical complication
- Application of topical haemostatic material on the liver resection wound
- Radiofrequency pre-coagulation of the liver resection wound except focal radiofrequency ablation of vessels as primary haemostatic treatment

Treatments

Dosing (number of patches) was according to the wound size. The trial treatment was applied once or twice if needed, intraoperatively.

The randomised trial treatment was applied immediately after randomisation and under aseptic conditions to all resection wound sites needing additional supportive haemostatic treatment, not only the "target bleeding site" with the most prominent bleeding, and particularly to any wound area left untreated by argon beam coagulator during resection of the liver. Vascular clamping of the liver (if applicable) was allowed, but was to be temporarily released for evaluation of haemostatic efficacy of the trial treatment.

Immediately after application of the trial treatment, the patches were lightly pressed against the wound area for 3 minutes. If haemostasis was not obtained at the "target bleeding site" 5 minutes after application of the trial treatment, a second application of the trial treatment was performed. Surgicel® Original could stay on the wound area or be removed according to surgical practice; however, TachoSil® was not to be removed at any time.

Concomitant medication

If anticoagulant therapy was stopped within 2 days prior to surgery, this was recorded in the concomitant medications section of the eCRF. Anticoagulation treatment related to surgery, and reversal thereof, and blood and liquid substitution were recorded separately.

Use of products containing thrombin or fibrinogen of any origin was not permitted during the trial. If any topical haemostatic material was applied before application of the trial treatment, the patient was to be excluded from the trial (see exclusion criteria, Section 9.3.2). After application of the trial treatment, no products containing thrombin or fibrinogen of any origin were to be applied.

Outcomes/endpoints

Primary efficacy endpoint:

Intraoperative haemostasis at target bleeding site within 3 minutes of application of allocated trial treatment

Secondary efficacy endpoints:

Intraoperative haemostasis at target bleeding site within 5 minutes of application of allocated trial treatment, and time to intraoperative haemostasis at target bleeding site within 10 minutes.

Treatment failure was defined as haemostasis not achieved after 10 minutes.

Safety evaluations included AEs, vital signs and clinical laboratory variables (including pregnancy test, haematology and blood chemistry. Immunogenicity testing to detect potential antibody formation and

viral serology were optional for patients ≥ 6 months of age.). Baseline values of INR, bilirubin, and creatinine were used to calculate the Model for End Stage Liver Disease (MELD) score.

Upon request from competent authorities (FDA), special attention was to be drawn to any suspicion of events, signs and symptoms of the following when conducting trials with investigational products such as TachoSil®:

- hepatic abscess or other surgically related infections,
- adhesions leading to bowel obstruction,
- surgically related thromboembolic events.

A hepatic abscess should have been suspected if the patient presented with abdominal pain, fever, chills, anorexia, tenderness and palpable mass etc.

Bowel obstruction should have been suspected if the patient presented with nausea, vomiting, abdominal pain, distension, constipation and inability to pass gas.

Thromboembolic events may present with numerous different symptoms. Hepatic portal vein thrombosis may have been suspected if the patient presented with abdominal pain, enlarged spleen, nausea, vomiting, diarrhoea, blood in stool, abdominal enlargement, and oesophageal varices, among others.

Analysis Plan

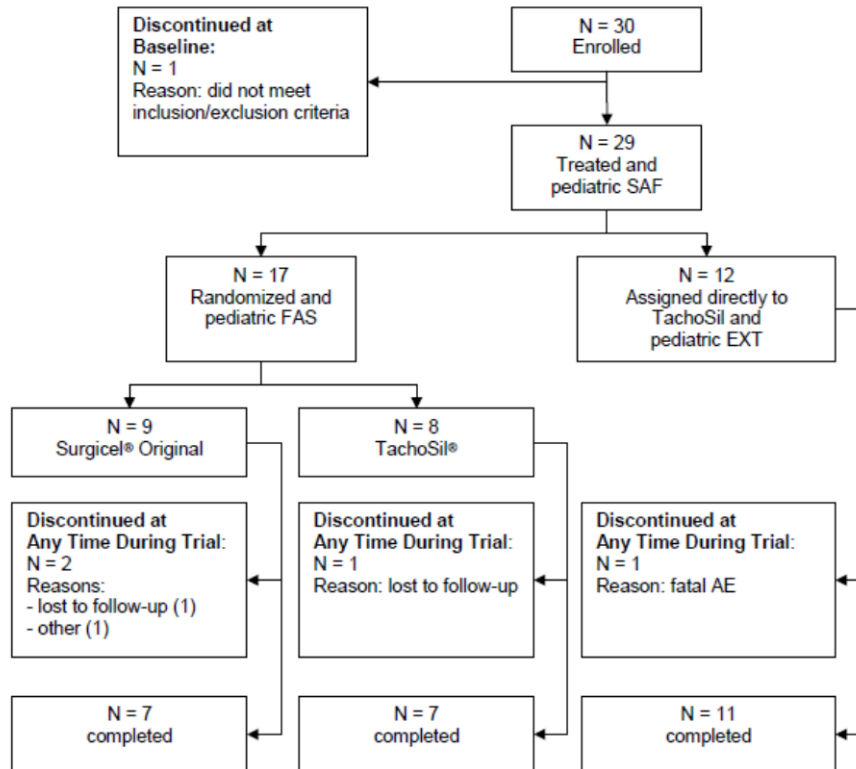
All 29 paediatric patients were included in the paediatric safety analysis set (paediatric SAF). 17 of the 29 treated patients, who were randomly assigned to treatment, were included in the paediatric full analysis set (paediatric FAS). The remaining 12 patients, who received treatment in the context of the paediatric extension part, were included in the paediatric extension set (paediatric EXT), which was a subset of the paediatric SAF.

Results

Recruitment/ Number analysed

Disposition data for paediatric patients are presented in Figure 3.

Figure 3 Disposition of Patients - All Pediatric Patients Enrolled



AE, adverse event; EXT, extension analysis set; FAS, full analysis set; SAF, safety analysis set.
Data Source: [Appendix 16.2](#), [Listings 26.2.1.1.1](#) and [26.2.3.1.1](#).

Baseline data

Demographics

Demographic data for the paediatric SAF population are summarised in Table 4.

Table 4 Demographic Characteristics of Pediatric Patients (Pediatric SAF)

Characteristic	TachoSil (N=20)	Surgicel Original (N=9)	Total (N=29)
Age, years			
n	20	9	29
Mean	4.58	3.77	4.33
SD	4.716	5.107	4.764
Median	2.00	1.83	2.00
Range	0.4, 13.0	0.4, 16.0	0.4, 16.0
Age group, n			
0-23 months	9	5	14
2-11 years	8	3	11
12-16 years	3	1	4
Sex, n (%)			
Male	10 (50.0)	4 (44.4)	14 (48.3)
Female	10 (50.0)	5 (55.6)	15 (51.7)

BMI, kg/m ²	TachoSil (N=20)	Surgicel Original (N=9)	Total (N=29)
n	19	7	26
Mean	17.49	16.57	17.24
SD	3.103	2.637	2.962
Median	16.80	16.30	16.70
Range	13.1, 24.7	13.9, 20.2	13.1, 24.7

Medical history and concomitant illness

Relevant medical history included 2 cases of gastrointestinal haemorrhage, 3 cases of cholecystectomy and 2 cases of portoenterostomy, all in the TachoSil® group (n=20).

Patient indication for liver resection in paediatric patients is summarised in Table 9.

Table 9 Indication for Liver Resection in Pediatric Patients (Pediatric SAF)

	TachoSil (N=20)	Surgicel Original (N=9)	Total (N=29)
Number of patients with indications for liver resections	20	9	29
Indication for liver resection	n (%)		
Malignant tumor	5 (25.0)	4 (44.4)	9 (31.0)
Benign lesion	1 (5.0)	0	1 (3.4)
Other	14 (70.0)	5 (55.6)	19 (65.5)
Cholestasis	0	1 (11.1)	1 (3.4)
Chronic hepatic failure	1 (5.0)	0	1 (3.4)
Congenital absence of bile ducts	4 (20.0)	3 (33.3)	7 (24.1)
Congenital hepatic fibrosis	1 (5.0)	0	1 (3.4)
Hepatic cirrhosis	2 (10.0)	0	2 (6.9)
Hepatic echinococcosis	1 (5.0)	0	1 (3.4)
Hepatic neoplasm malignant	0	1 (11.1)	1 (3.4)
Hyperoxaluria	1 (5.0)	0	1 (3.4)
Langerhans' cell histiocytosis	1 (5.0)	0	1 (3.4)
Portal vein thrombosis	3 (15.0)	0	3 (10.3)

N, total number of patients in the group; n, the number of patients within the analysis set. FAS.

Concomitant illness was reported for a total of 26 (89.7%) paediatric patients: 18 (90.0%) patients in the TachoSil® group and 8 (88.9%) patients in the Surgicel® Original treatment group. In the TachoSil® group, the most frequently reported concomitant illness PTs were splenomegaly and

thrombocytopenia (each 30.0% of patients), anaemia and gastroesophageal reflux disease (each 25.0% of patients). In the Surgicel® Original group, the most frequently reported concomitant illness PTs were neurosensory deafness, hepatic cirrhosis, drug hypersensitivity, and food allergy (each 22.2%).

Efficacy results

A total of 17 (of 20) patients treated with TachoSil® reached the primary endpoint of haemostasis within 3 minutes. The secondary endpoint, haemostasis within 5 minutes, was reached by 19 TachoSil® patients and all 20 patients achieved haemostasis within 10 minutes.

These results were comparable to those of the adult study population.

For the paediatric FAS, a summary of time to haemostasis of TachoSil® compared to Surgicel® is displayed in Table 17.

Table 17 Summary of Time to Hemostasis in Pediatric Patients, (Pediatric FAS)

	TachoSil (N=8)		Surgicel Original (N=9)	
	Total n (%)	Cumulative Total n (%)	Total n (%)	Cumulative Total n (%)
Time to hemostasis (minutes)				
[0-3] (primary outcome variable)	7 (87.5)	7 (87.5)	4 (44.4)	4 (44.4)
(3-4]	0	7 (87.5)	2 (22.2)	6 (66.7)
(4-5]	0	7 (87.5)	1 (11.1)	7 (77.8)
(5-8]	1 (12.5)	8 (100.0)	1 (11.1)	8 (88.9)
(8-9]	0	8 (100.0)	0	8 (88.9)
(9-10]	0	8 (100.0)	0	8 (88.9)
>10	0	8 (100.0)	1 (11.1)	9 (100.0)

FAS, full analysis set; N, total number of patients in the group; n, the number of patients within the analysis set. Missing refers to all patients who had no recorded time to hemostasis. For time ranges, "]" represents inclusive and "(" represents exclusive.

Data Source: Section 14, Table 24.2.1.1.

Treatment exposure

Of the 20 patients treated with TachoSil®, 19 had one application of treatment, 1 had a second one. In 16 patients up to one patch was applied, in the remaining 4 patients a maximum of two patches were used for treatment.

Safety results

Adverse events (AEs)

AEs occurred in all of the 20 TachoSil® study subjects. A total of 156 AEs were reported, thereof 34 serious AEs occurred in 12 of the 20 subjects.

A summary of AEs in paediatric patients is presented in Table 21.

Table 21 Summary of Adverse Events in Pediatric Patients (Pediatric SAF)

	TachoSil (N=20)		Surgicel Original (N=9)		Total (N=29)	
	n (%)	E	n (%)	E	n (%)	E
Adverse events	20 (100)	156	9 (100)	55	29 (100)	211
Serious adverse events	12 (60.0)	34	4 (44.4)	11	16 (55.2)	45
Related adverse events	0	0	0	0	0	0
Serious related adverse events	0	0	0	0	0	0
Not related adverse events	20 (100)	156	9 (100)	55	29 (100)	211
Mild adverse events	19 (95.0)	125	8 (88.9)	45	27 (93.1)	170
Moderate adverse events	11 (55.0)	19	4 (44.4)	6	15 (51.7)	25
Severe adverse events	4 (20.0)	12	2 (22.2)	4	6 (20.7)	16
Adverse events leading to death	1 (5.0)	1	0	0	1 (3.4)	1
Adverse events leading to withdrawal	1 (5.0)	1	0	0	1 (3.4)	1
Serious adverse events other than death	12 (60.0)	33	4 (44.4)	11	16 (55.2)	44

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

Data Source: Section 14, Table 24.3.2.1.

The AE PTs most frequently reported for patients in the TachoSil® group were pyrexia (9 [45.0%] patients), anaemia (6 [30.0%] patients), and diarrhoea (4 [20.0%] patients). The AE PT most frequently reported for patients in the Surgicel Original® group was pyrexia (5 [55.6%] patients). No other PT was reported for more than 2 patients in the Surgicel® Original group.

None of these AEs were considered treatment related by the investigator.

One AE of an exsanguination leading to death occurred, which was also not considered related to treatment with TachoSil®.

A separate summary of adverse events of special interest in paediatric patients is depicted in Table 28.

Table 28 Summary of Adverse Events of Special Interest in Pediatric Patients by Treatment (SAF)

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

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.

Data Source: Section 14, Table 24.3.2.12.

Assessor's comment:

A total of 156 AEs were reported in the paediatric study population, including 34 serious AEs and 1 AE leading to death as well as 12 AEs of special interest. None of these AEs was considered related to study treatment by the investigator.

However, especially for the adverse events of special interest, study drug relatedness would at least to some degree be assumed as a matter of principle. Therefore, the MAH is asked to submit the causality assessments for these AEs of special interest. Additionally, the causality assessment for the AE leading to death should be provided.

Laboratory values & vital signs

Summary statistics, shift plots and individual listings of laboratory values and vital signs are provided by the MAH.

Several patients in each treatment group had clinically significant abnormal values at certain visits and several patients in each treatment group had AEs related to abnormal results. However, the only SAEs related to abnormal laboratory results were febrile neutropenia (1 patient each in the TachoSil® group and Surgicel® Original group). Neither of these SAEs was considered by the investigator to be related to treatment.

Immunogenicity

Informed consent for immunogenicity testing was provided for 4 (50.0%) patients in the TachoSil® group. No paediatric patient included in the immunogenicity testing developed antibodies to equine collagen, fibrinogen, albumin, or thrombin.

Viral serology

None of the paediatric patients showed a positive result after viral serology testing.

2.3.3. Discussion on clinical aspects

Following Article 46 of Paediatric Regulation (EC) No. 1906, the Clinical Trial Report TC-2402-040-SP for the study "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" was submitted by Takeda Austria GmbH.

TachoSil® is a ready-to-use degradable surgical patch developed for topical use consisting of a dry foamed collagen carrier of equine origin, coated with human fibrinogen and human thrombin. As comparator product, Surgicel® Original was used, which is a standard haemostatic agent consisting of oxidised regenerated cellulose.

A paediatric part with 29 subjects was included in the study. Of these, 17 were randomly assigned to treatment (8 to TachoSil® and 9 to Surgicel®), whereas 12 were enrolled in the context of an extension trial and exclusively treated with TachoSil®, so that in total 20 paediatric patients were treated with TachoSil®.

Indication for liver resection in the 20 paediatric subjects treated with TachoSil® included, inter alia, malignant tumor, portal vein thrombosis, hepatic cirrhosis, congenital hepatic/biliary disease.

Randomisation to TachoSil® or Surgicel® Original was conducted during surgery, after completion of primary haemostatic treatment. Trial treatment was applied to all resection wound sites needing additional supportive haemostatic treatment (not only the “target bleeding site”). Dosing (number of patches) was according to the wound size.

For efficacy evaluation, intraoperative haemostasis at the target bleeding site within 3, 5 and 10 minutes after application of allocated trial treatment was assessed.

All 20 paediatric subjects treated with TachoSil® achieved haemostasis within 10 minutes, and 17 of them already within 3 minutes after product application.

Adverse events (AEs) occurred in all 20 paediatric TachoSil® study subjects. In total, 156 AEs were reported, including 34 serious AEs with 1 AE of an exsanguination leading to death, furthermore 12 AEs of special interest (adhesions, hepatic abscess, thromboembolic events). None of these AEs was considered related to study treatment by the investigator.

However, especially for the adverse events of special interest, study drug relatedness would at least to some degree be assumed as a matter of principle. Therefore, the MAH is asked to submit the causality assessments for these AEs. Additionally, the causality assessment for the AE leading to death should be provided.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

From the paediatric study data presented by the MAH, no new information beyond what is already reflected in the current valid SmPC can be drawn. Nevertheless, for a final assessment, some information as detailed in the list of questions below is still missing.

Recommendation

Fulfilled:

Not fulfilled:

Based on the data submitted, the MAH should provide additional information as part of this procedure as outlined below. (see section IV "Additional clarifications requested")

4. Additional clarifications requested

A total of 156 AEs were reported in the paediatric study population, including 34 serious AEs and 1 AE leading to death as well as 12 AEs of special interest. None of these AEs was considered related to study treatment by the investigator.

However, especially for the adverse events of special interest, study drug relatedness would at least to some degree be assumed as a matter of principle. Therefore, the MAH is asked to submit the causality assessments for these AEs of special interest. Additionally, the causality assessment for the AE leading to death should be provided.

The timetable is a 30 day response timetable with clock stop.

5. Rapporteur's assessment of the MAH's responses

Question 1

A total of 156 AEs were reported in the paediatric study population, including 34 serious AEs and 1 AE leading to death as well as 12 AEs of special interest. None of these AEs was considered related to study treatment by the investigator.

However, especially for the adverse events of special interest, study drug relatedness would at least to some degree be assumed as a matter of principle. Therefore, the MAH is asked to submit the causality assessments for these AEs of special interest. Additionally, the causality assessment for the AE leading to death should be provided.

MAH's responses

The MAH submits a tabular list of all SAEs and Adverse Events of Special Interest, which occurred in a total of 14 subjects during the study, including the fatal case. A causality assessment, which has been re-reviewed by the company for the purposes of this procedure, is enclosed for each case.

Assessment of the MAH's responses

Following the provided causality assessments, events were coincidental with other conditions being more likely the cause (e.g. underlying stenosis of the suprahepatic vena cava in the event of hepatic artery thrombosis), or relatedness to TachoSil® was biologically implausible (e.g. post procedural bile leak) or latency of onset after product administration was considered too long to be indicative of a causal relationship.

Conclusion

The causality assessments, which were provided for all SAEs and adverse events of special interest by the MAH, are considered reasonable and comprehensive.

Therefore, the **issue is** regarded as **resolved**.

6. Rapporteur's overall conclusion on the MAH's responses and recommendation

Recommendation

Fulfilled: Upon request for additional information, satisfactory response was provided by the MAH. Therefore, the procedure is considered fulfilled.