23 February 2023
EMA/CHMP/133841/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TachoSil

International non-proprietary name: human thrombin / human fibrinogen

Procedure No. EMEA/H/C/000505/II/0117

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AMISA	Adjustable Minimally Invasive Surgery Applicator
ATSS	Amisa TachoSil System
CI	Confidence Interval
CF	Cystic Fibrosis
CSF	CerebroSpinal Fluid
CT	Computed Tomography
EMA	European Medicines Agency
ENT	Ear, Nose, Throat specialist
EU	European Union
FAS	Full Analysis Set
FTCCP	Fibrinogen/Thrombin-Coated Collagen Patch
IBD	International Birth Date
I.U	International Units
ISS	Integrated Summary of Safety
LOS	Length of Stay (in hospital)
OR	Odds Ratio
NEC	Necrotising Entero Colitis
NSS	Nephron Sparing Surgery
PBRER	Periodic Benefit-Risk Evaluation Report
PRBC	Packed Red Blood Cell
PT	Prothrombin
USSR	United Socialist Soviet Republic
VATS	Video-Assisted Thoracoscopic Surgery

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Corza Medical GmbH submitted to the European Medicines Agency on 30 April 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of children aged 1 month to 18 years, based on available bibliographical data, results from study TC-2402-040-SP which compared TachoSil with Surgicel Original as adjunct to primary surgical treatment in both adult and paediatric subjects, and results from Study TC-019-IN; a prospective, uncontrolled study in paediatric subjects. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the product information. Version 0.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 April 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	12 August 2022
PRAC Rapporteur Assessment Report	19 August 2022
PRAC members comments	24 August 2022
Updated PRAC Rapporteur Assessment Report	25 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	22 December 2022
PRAC Rapporteur Assessment Report	3 January 2023
PRAC members comments	4 January 2023
Updated PRAC Rapporteur Assessment Report	5 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur Assessment Report	19 January 2023
2nd Request for supplementary information (RSI)	26 January 2023
CHMP/PRAC Rapporteurs Assessment Report	8 February 2023
PRAC members comments	13 February 2023
CHMP members comments	13 February 2023
CHMP/PRAC Rapporteurs Assessment Report	16 February 2023
CHMP opinion	23 February 2023

2. Scientific discussion

2.1. Introduction

TachoSil is a ready-to-use degradable surgical patch developed for topical use to support intraoperative haemostasis and tissue sealing. TachoSil was approved by the European Commission in 2004.

The purpose of this type II variation is to request to expand the currently approved indications of TachoSil in adults for use in the paediatric population (see under 2.1.1).

This application is mainly based on available publications reporting data with off-label use of TachoSil in children. As supportive information, the applicant further referred to data from paediatric patients from study TC- 2402-040-SP and from a comparative study in adult and paediatric patients undergoing hepatic resection surgery (Study TC-019-IN). Data from Study TC-019-IN, a prematurely stopped prospective, uncontrolled study in paediatric subjects, were also included into a pool of paediatric data.

2.1.1. Problem statement

Disease or condition

Haemostasis is a rather complex process. The injury of a blood vessel triggers the following sequence of events: (i) vessel constriction to reduce blood flow; (ii) adherence of circulating platelets to the vessel wall at the site of the trauma; and (iii) platelet activation and aggregation, coupled with an intricate series of enzymatic reactions involving coagulation proteins that produce fibrin to form a stable haemostatic plug. The aim of all haemostatic agents (Has) is to act by imitating, promoting, or bypassing specific steps of the coagulation cascade. The haemostatic system is incompletely developed at birth and matures throughout infancy. Although all key components of the haemostatic system are present at birth, important quantitative and qualitative differences exist between neonates and adults. The concentration of clotting factors in human blood changes after birth, until adulthood, at different levels (as published in the Meta-Analysis by Toulon et (2016), Developmental haemostasis: laboratory and clinical implications. Int. Jnl. Lab. Hem., 38: 66-77), Prothrombin (PT, Factor II) and Fibrinogen (Factor I), coagulation factors of the last stage of the blood clotting cascade, reach their normal level within the first year after birth.

The current indication (Section 4.1 SmPC) for TachoSil in adults covers "supportive treatment in surgery, improvement of haemostasis, promotion of tissue sealing, suture support in vascular surgery where standard techniques are insufficient, and supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery".

As part of the present type II variation the MAH applied to expand the above-mentioned indication of TachoSil for use in the paediatric population. The claimed indication was as follows: "TachoSil is indicated in adults and children aged 1month to 18 years for supportive treatment in surgery, for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery (see section 5.1)."

The recommended indication is as follows: "TachoSil is indicated in adults and children from 1 month of age 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 indicated in adults for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery (see section 5.1)." (see SmPC section 4.1).

Epidemiology

Based on national data from England, there were an estimated 157,046 operations in which TachoSil may be appropriate in a total population of 50.762 million in 2005. This extrapolates to approximately 1.519 million operations in which TachoSil may be appropriate for the 27 countries EU population of 491.024 million in 2005.

Based upon data from a registry of vascular surgery activity in Spain (1996-2011), the mean number of vascular surgical procedures performed per hospital per year was 742 [Lozano FS et al, Monitoring the practice of vascular surgery: findings from a national registry (1996-2011), World J Surg 2014;38(1):241-4]. For select vascular surgical procedures, based upon data collected from national and regional vascular registries from several countries in Europe, the volume or rate of reported procedures performed was as follows: infrainguinal bypass (2.3-24.6 per 100,000 population, 2005-2009), carotid artery procedures (53,077, 2005-2010), and abdominal aortic aneurysm repair (40,848, 2005-2009).

Management

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledges, and/or electrocautery. Absorbable haemostatic agents such as bovine gelatine power and sponges, and haemostatics agents made from bovine collagen and oxidised cellulose are also used for stopping bleeding. Additionally, products containing thrombin and/or fibrinogen are used to assist body´s natural clotting mechanism to achieved haemostasis. The versatility of fibrin sealant is due to its capacity to cause blood to clot, creating a sealing barrier as well as gluing tissues together.

2.1.2. About the product

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.

Predecessors of TachoSil were TachoComb and TachoComb H, both containing aprotinin derived from bovine lung. Aprotinin was used for extending the persistence of fibrin clots. However, due to the risk of life-threatening anaphylaxis, and due to bovine origin, aprotinin was further disfavored (see below).

TachoComb is marketed since 1992 in many countries; last batch was manufactured in August 2011, for Japan and Korea. Brand name has been kept and is still used in some former USSR countries, although with the new TachoSil formulation. TachoComb H was marketed amongst others in Germany and Austria from 2001 to 2005, replacing TachoComb; last batch was manufactured in September 2011, also for Japan. TachoSil stands for the currently approved formulation, approved by EMA in June 2004; synonyms during development were "TachoComb S" and "TachoComb TC-S". TachoSil differs from its predecessors by a successive removal of bovine sourced components (bovine thrombin and bovine aprotinin) and by lacking the antifibrinolytic aprotinin.

Table 1 Origin of the Components of TachoSil and its Predecessors

	Collagen	Fibrinogen	Thrombin	Aprotinin
TachoComb *	yes	yes	bovine	yes
TachoComb H **	yes	yes	human	yes
TachoSil ***	yes	yes	human	no

* **TachoComb:** marketed since 1992 in many countries; last batch (613530A) was manufactured in August 2011, for Japan and Korea. Brand name has been kept and is still used in some former USSR countries, although with the new TachoSil formulation.

** **TachoComb H:** marketed amongst others in Germany and Austria from 2001 to 2005, replacing TachoComb; last batch was manufactured in September 2011, also for Japan.

*** **TachoSil:** New formulation, submitted and approved by EMA in June 2004; synonyms during development were named "TachoComb S" and "TachoComb TC-S"

TachoSil is a further development of TachoComb and TachoComb H, which were in clinical use for several years in a range of countries. Some nonclinical data on these predecessor product versions were transferable to the current TachoSil formulation. TachoSil differs from its predecessors by a successive removal of bovine sourced components (bovine thrombin and bovine aprotinin) and by lacking the antifibrinolytic aprotinin. Of note, the predecessor products TachoComb and TachoComb H differ from TachoSil in bovine components and the addition of aprotinin. Unfortunately, the brand name "TachoComb" has been maintained in some countries – according to the MAH despite changing the formulation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No CHMP advice was sought. Paediatric Investigation Plan (PIP) for TachoSil is not in the Scope of the Paediatric Regulation due to the approval date of TachoSil (2004) which was before the entry into force of the paediatric Regulation.

Similar products have been subject to PIP-procedures with recommendation of controlled studies in paediatric subjects.

The focus of this application is based on the following points:

- Available publications, reporting safety and efficacy data in patients aged 1 day to 19.8 years with off-label use of TachoSil;
- Nearly 18 years post-marketing safety and efficacy data;
- Cumulative exposure of over 10 million patients worldwide (as per June 2021), with a 0.013% incidence of adverse events;
- Study TC- 2402-040-SP as supporting data: a randomized, open-label, parallel group, multi-centre trial, to compare the efficacy and safety of TachoSil versus Surgicel Original for secondary treatment of local bleeding in adult and paediatric patients undergoing hepatic resection surgery; submitted to the FDA in 2014 and based on which a paediatric indication was granted in the US. This study fulfilled a commitment stated in the 2010 FDA approval letter, to conduct a deferred paediatric study for use of TachoSil as an adjunct to haemostasis in paediatric patients 0-16 years undergoing hepatic resection surgery. Since 2015, TachoSil has been used in the US in patients from 1 month of age.
- Data from Study TC-019-IN, a prematurely stopped prospective, uncontrolled study in paediatric subjects, were also included into a pool of paediatric data

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.2. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Fibrinogen and Thrombin are not expected to pose a risk to the environment in accordance with the Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

In animal studies, TachoSil biodegrades after administration to a wound surface, with few remnants left after 13 weeks. Complete degradation of TachoSil was seen in some animals 12 months after its administration to a liver wound, whereas small remnants were still observed in others. The degradation was associated with infiltration of granulocytes and formation of resorptive granulation tissue encapsulating the degraded remnants of TachoSil. No evidence of local intolerability has been observed in animal studies.
From the experience in humans, there have been isolated cases where remnants were observed as coincidental findings with no signs of functional impairment. Single dose toxicity studies in different species of animals have shown no signs of acute toxic effects.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Human Fibrinogen/Human Thrombin.

Considering the above data, Human Fibrinogen/Human Thrombin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Biopharmacokinetics

TachoSil is intended for topical use during surgical interventions to support vascular sealing to provide adjunct local haemostasis in surgery. Therefore, considerations of bioavailability do not apply.

2.3.2. Pharmacodynamics

Mechanism of action

Following contact with physiological fluids (e.g., blood, lymph), or physiological saline solution, the coagulation factors of the TachoSil coating dissolve and partly diffuse into the wound surface. Subsequently, the fibrinogen-thrombin reaction takes place, which initiates the last step of the coagulation cascade. Fibrinogen is converted into fibrin monomers that spontaneously polymerise into fibrin strands. These form a viscous and elastic clot, which attaches the patch tightly onto the wound surface.

The fibrin is then cross linked by endogenous factor XIII, creating a firm, mechanically stable network with good adhesive properties; therefore, it provides not only haemostasis, but sealing as well, independent of the subject’s own coagulation system.

Fibrin sealants/haemostatics are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis; besides, the fibrin matrix serves as scaffolding for fibroblast migration, which is important for the tissue healing process.

After moistening, the TachoSil patch becomes pliable and can be moulded to the tissue surface. TachoSil exhibits extensibility characteristics to accommodate for the physiological movements of tissues and organs.

2.3.3. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted as part of the current application procedure.

2.3.4. Conclusions on clinical pharmacology

No new clinical pharmacology data were submitted as part of the current application procedure. TachoSil differs from TachoComb and TachoComb H regarding Aprotinin as an additional active substance, and the successive replacement of bovine components. The medicinal products are therefore not considered to be interchangeable. This has implications on the clinical data provided below.

2.4. Clinical efficacy

2.4.1. Main study

No new study results have been submitted. The applicant provided a discussion on data previously submitted data in the scope of post-authorisation measures.

Study TC-019-IN (hepatic resection surgery):

Study TC-019-IN was a prospective, multi-centre, non-controlled, phase III-b study of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. For the primary (and only) efficacy endpoint of time to haemostasis (ITT, intention to treat population), 13 of 16 subjects (81.3% [95% CI: 61.8-100%]) obtained haemostasis at 3 minutes after application of TachoSil. One subject obtained haemostasis at 8 minutes after application of TachoSil. Two subjects failed to achieve satisfactory haemostasis within 10 minutes, which necessitated alternative haemostatic measures.

The study was halted by Takeda after a period of 16 months, and after 16 of planned 40 children had been enrolled. The unavailability of hospital records and the complexities of multidisciplinary critical care, made comprehensive and consistent data recording in the case report form (CRF) impractical, and monitoring, including source data verification, impossible for significant periods. These circumstances resulted in the late reporting of a serious adverse event (SAE). This event and the difficulty working to Good Clinical Practice (GCP) led Takeda to halt the study. Additionally, it became apparent during this review that a study in this subject population would primarily collect safety data related to the underlying disease/procedure. The study was discontinued and the findings for the subjects included to that point were to be reported.

Study TC-2402-040-SP (hepatic resection surgery, paediatric population):

Study TC-2402-040-SP was a randomized, open-label, parallel group, multi-centre trial, to compare the efficacy and safety of TachoSil versus Surgicel Original for secondary treatment of local bleeding in adult and paediatric patients undergoing hepatic resection surgery. For the primary efficacy endpoint, the proportion of subjects in the paediatric FAS (Full analysis set, consisting of all 17 paediatric patients who were randomly assigned to treatment) who achieved haemostasis within 3 minutes was 87.5% (95% CI: 47.3, 99.7) in the TachoSil group and 44.4% (95% CI: 13.7, 78.8) in the Surgicel Original group. For the paediatric FAS, the proportion of subjects who achieved haemostasis within 5 minutes was higher in the TachoSil group (87.5%) than in the Surgicel Original group (77.8%).

Median (range) observed time to haemostasis was 3.0 (3, 8) minutes in the TachoSil group and 3.5 (3, 8) minutes in the Surgicel Original group (FAS).

Pooled Analysis

The applicant furthermore provided a pooled analysis based on the paediatric patients from the above two mentioned studies TC-019-IN and TC-2402-040-SP, which is called the "Paediatric Study Pool". A total of 45 paediatric subjects were included in the paediatric study pool: 36 in the TachoSil group (8 randomised and 12 from the extension part from study TC-2402-040-SP, as well as 16 patients enrolled in TC-019-IN) and 9 in the comparator group (from study TC-2402-040-SP, all randomised).

Table 2: Summary of results from both paediatric populations studied in TC-2402-040-SP and TC-019-IN. Adult population from study TC-2402-040-SP included for comparison, FAS – full analysis set, SAF – safety analysis set, CI – confidence interval

Proportion of patients achieving haemostasis within 3 minutes from application			
TC-2402-040-SP			TC-019-IN
Adults (FAS n=114)	*Children*		Children n=16
	FAS n=8	SAF n=20	
80.7% 95% CI, 72.3 – 87.5	87.5% 95% CI, 47.3 – 99.7	85% 95% CI, 62.1 – 96.8	81.3% 95% CI, 61.8 – 100.0

Bibliographic data

To support the extrapolation concept, the following data sources were used:

- 11 clinical trials from TachoSil development program: 9 prospective, randomised controlled trials on adult population, 1 non-interventional, prospective surveillance trial on adult population, one prospective, one-arm trial on paediatric population and one paediatric sub-study partly prospective, randomised controlled trials and partly one-arm. In total, 5246 patients were enrolled, of which 4223 received TachoSil treatment.

These data were considered adequate and sufficient to gain marketing authorisation for TachoSil for adult population in EU and both, adult and paediatric population in USA. Paediatric trials included relatively low number of subjects (45 total, 36 of which received TachoSil treatment), which is expected for paediatric studies. The 95% confidence interval for point estimates were wide, thus the evidence from paediatric trials is considered limited. Ten trials were referenced to published papers, one to ClinicalTrials.gov. In general, these studies supported the efficacy of TachoSil, as well as superiority of TachoSil over standard treatment in hepatic, renal and cardiac surgeries.

- Twelve (12) scientific publications confirming the use of similar class of medicinal products (B02BC30, local haemostatics, combinations) in paediatric population (total of 1292 children aged 1 day to 18 years received fibrin sealant treatment).
- Seven papers presented retrospective chart/cases review, 2 were prospective randomised (1 open-label, 1 double blind), 3 others were prospective studies (either open label, non-randomised or observational cohort study). The quality of evidence from these publications varies and is from low to high, depending on the study design. Overall, these studies provide evidence on the use of similar medicinal products in paediatric population and support its efficacy.
- Fifteen (15) publications from clinical trials concerning the development of haemostatic system in children and similarities/differences between target and reference population. Thirteen studies were prospective, non-interventional, with high quality of evidence. Two other studies were retrospective chart review, with moderate quality of evidence. These studies showed that despite some differences in coagulation and anticoagulation parameters between children and adults, the effective haemostatic system was maintained in paediatric population and observed differences should be considered physiologic.

- Three (3) publications confirming the use of TachoSil in paediatric population: one retrospective study and 2 case series presentation. The quality of evidence is low (case series) to moderate (retrospective study). The retrospective study (n=117) and one case study (n=6) concerned the use of TachoSil during heart surgery.
- Two (2) research articles comparing TachoSil with TachoComb: 1 randomised double blind clinical trial and 1 animal experimental study, quality of evidence is high and moderate, respectively. Noninferiority of TachoSil was demonstrated.
- One (1) case study concerning TachoSil related granuloma, 1 retrospective study on TachoSil in dural repair and one post market surveillance study on TachoSil safety and efficacy – The quality of evidence is low (case study) to moderate (retrospective and surveillance study).

Supporting data sources: 4 review papers on the development of haemostatic system in children, 25 human and 4 animal research papers investigating the mechanisms of coagulation in humans, functions of cardiovascular system, immunological response plus 7 reviews on these topics, 1 research article on the incidence of colon cancer, 1 review article on narrow therapeutic index, 4 clinician's statements and EMA assessment report.

2.4.2. Discussion on clinical efficacy

TC-019-IN:

The clinical trial report of study TC-019-IN, an open-label, non-controlled prospective, multi-centre, phase III-b study of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation, was previously submitted in order to fulfil a post-authorisation commitment (Follow-up measure (FUM) 012). Respective procedure is referred to (EMEA/H/C/505, EU/1/04/277/001-004, 2008).

Although fourty children were planned to be enrolled in the study, only 16 were enrolled when the study was discontinued due to difficulties to comply with GCP requirements. Median age was 15 (2.5 – 147.5) months. The open design of the study, the application of TachoSil on graft tissue and the extremely severe clinical situation of the children restricted the evidence of the gained data. Due to the very small sample size, the 95% confidence interval for the point estimate of the proportion of obtaining haemostasis at 3 minutes after application of TachoSil was very wide and hence the uncertainty in the study results was large. Overall, a profound evaluation of efficacy could not be performed based on these data. No amendment to the SmPC were recommended based on the evaluation of the data in the respective FUM012 procedure.

Study TC-2402-040-SP

Study TC-2402-040-SP was a randomized, open-label, parallel group, multi-centre trial, to compare the efficacy and safety of TachoSil versus Surgicel Original for secondary treatment of local bleeding in adult and paediatric patients undergoing hepatic resection surgery. The study was subject to an Article 46 procedure (EMEA/H/C/000505/P46 039).

In the paediatric part including 29 subjects, 17 were randomly assigned to treatment (8 to TachoSil and 9 to Surgicel), whereas 12 were enrolled open-label in the context of an extension trial and exclusively treated with TachoSil. In total 20 paediatric patients were treated with TachoSil. Age-range was 0.4 to 13.0 years for the TachoSil group. Seventeen out of 20 paediatric subjects treated with TachoSil achieved haemostasis within 3 minutes after product application versus 4 (of 9) in the Surgicel-group. Median observed time to haemostasis was 3.0 minutes in the TachoSil group and 3.5 minutes in the Surgicel Original group, representing quite similar values.

Also in this study, due to the small sample size (n=17), the confidence interval for the estimated proportion of obtaining haemostasis at 3 minutes after application of TachoSil, the primary efficacy endpoint, was very wide and hence the uncertainty large.

No SmPC amendment was recommended in the respective Article 46 procedure.

Of note, age-range was between 4 months and 13 years in this study. Data on patients aged 13-18 years are not available.

Pooled Analysis

In the so-called "integrated analysis", the applicant just simply pooled the results of the two studies, without weighting or accounting for different variances in the two trails. Due to its post-hoc nature as well as heterogeneities in the designs of the two pooled trials, these pooled results are subject to a lot of uncertainty. Additionally, even after pooling, if the above-mentioned uncertainties are not taken into account, the confidence intervals were quite large and the pooled results did not provide any new evidence compared to the results of the individual studies.

Bibliographic data:

In total, 20 Articles from the scientific literature have been provided.

5 Articles referred to TachoComb containing aprotinin, and therefore are not relevant for the present application considering the different medicinal products. One of them covers 1633 patients with Tonsillectomy. One article (Krivchenia D et al) was in Russian language, containing only a brief statement in English language ("trust the safety and efficacy of Tachocomb platelets application in pediatric surgery"), and therefore difficult to consider. One article is a citation of the other (Kieran et al and Mele et al). One article is the publication of the FUM-study (Mirza et al). One article describes the use of TachoSil moistened with gentamicin, a non-approved use - therefore also not considered relevant for the current application.

Two case-reports of neurosurgery described use of a combination of TachoSil with an approved fibrin glue – thus not providing clear evidences for TachoSil alone (Keinänen et al and Pennacchietti et al).

Most of the remaining articles described interesting case-reports or case-series in special circumstances (bilateral Wilms-tumor, Cystic fibrosis, Liver transplantation, ruptured neuroblastoma), rare disease (Adams-Oliver-Syndrome), and specific surgical techniques (Minimally invasive procedures, intracranial bullet removal, neuro-navigation technique, nephron-sparing surgery, bladder-neck surgery).

Further, experimental approaches (prevention of lymphatic leaks, necrotising enterocolitis with zebra-technique) were presented.

Data quality was of considerably differing levels (letter to the editor, retrospective chart reviews, single case-reports, prospective study – FUM-study).

Overall, the literature compilation is considered to be interesting in the sense of surgical progress. Five articles and the majority of the data were collected from patients treated with TachoComb, containing aprotinin. Hence these data are not to be considered supportive for present TachoSil application. Specific clinical data in paedaitric would have been expected in line with the clinical guideline. The company was asked to perform an extrapolation exercise.

Extrapolation exercise:

Based on the review of the existing knowledge on developmental haemostasis, clinical data on TachoSil in adult population and limited information from paediatric patients, an extrapolation concept was developed and assumed that the extrapolation of efficacy and safety of TachoSil from reference population (adults) to target population (paediatrics) is justified. The data concerning similarities and differences regarding

the patient condition ("disease", herein postoperative wound and process of its healing), response to treatment and pharmacology were reviewed and integrated and are generally considered consistent across sources. The differences found between target and reference population are not expected to affect the response to treatment.

Since TachoSil patch is a locally applied medicinal product and the amount of the patch required to be applied should be adequate to the wound size and underlying clinical need for the patient, no exposure effect is expected to affect the outcome of a treatment. Although, patients' weight and wound size will likely to be different between populations, exposure-response relationship is not expected to differ due to local modality of application, and adjustment the size of a patch to wound size and bleeding rate.

Taken together, it is firstly concluded that the apparently substantial differences in haemostasis physiology with pronounced numerical differences in plasma levels of most haemostatic proteins and functional readouts provide sound justification for an exclusion of neonates (i.e. children up to 1 month of age) from the requested paediatric extension of indication.

Secondly, it is noted that the question of the exact age at which the coagulation system can be regarded fully established cannot be answered conclusively. However, current literature supports the notion of most pronounced changes towards adult values within the first month of life and indicates a trend of stabilisation beyond the 1-month boundary. Moreover, TachoSil's composition and its mechanism of action argue for a rather minor impact of the patient's own haemostatic system and the few remaining potentially relevant aspects of development are not considered likely to exert any significant age-related impact beyond the first month of life.

Hence, overall, the proposed definition of a lower age limit of 1 month in the requested paediatric extension of indication (i.e. section 4.1 of the TachoSil SmPC) is considered acceptable.

2.4.3. Conclusions on the clinical efficacy

Both available clinical studies with paediatric involvement (TC-019-IN, TC-2402-040-SP) rely on data from hepatic surgery in a narrow patient population with challenging results. Both have been submitted and assessed in earlier procedures (FUM and Article 46). From a biostatistics' point of view, for both studies confidence intervals for the primary efficacy endpoint were very wide, and hence the uncertainty large. Regarding the pooled data, due to post-hoc nature and heterogeneity of the trial-designs, results are even more subject to uncertainty. Bibliographic data reflect a heterogeneous collection, not clearly covering the targeted clinical use of TachoSil. Although positive statements regarding efficacy are found in several publications, these data cannot replace convincing clinical-study-results according to the clinical guideline.

Overall and mainly based on the extrapolation exercise the requested paediatric extension of indication is considered acceptable for vascular surgeries. Furthermore, it has been agreed on a brief reflection of available paediatric data in section 5.1 and removal of the statement *"TachoSil is not recommended for use in children below age 18 years due to insufficient data on safety and efficacy."* in section 4.2 of the TachoSil SmPC

2.5. Clinical safety

Introduction

The MAH presented a pooled safety analysis. 36 paediatric patients have been exposed to TachoSil in clinical studies (TC-2402-040-SP and TC-019-IN).

Patient exposure

In the study pool of 45 paediatric subjects, 36 (8 randomised, 28 open label) were accounted to the TachoSil group and 9 (randomized) to the Comparator group. The majority of paediatric subjects used ≤1 patch (25 [69.4%]) or >1 to 2 patches (8 [22.2%]). The minimum number of patches used in a single paediatric subject was 0.25 and the maximum in a subject treated with TachoSil was 2 patches.

Age range in the TachoSil group was 0-13 years.

Adverse events

The majority of subjects in both treatment groups experienced TEAEs that were considered mild or moderate in intensity, all of which were considered not related to study treatment. Incidence of severe adverse events was approximately the same across treatment groups and only 20 of 272 total adverse events were considered severe.

Serious adverse event (SAE)/deaths/other significant events

SAEs were reported by 17 of 34 subjects in the TachoSil group and 4 of 9 subjects in the Comparator group. No subjects in either treatment group experienced an SAE that was considered related to study treatment.

Events of special interest (ESI) were presented for the paediatric study pool in comparison to the comparator Surgicel.

Table 3: Overall summary of subjects with ESIs by treatment (paediatric study pool)

Medical Category	TachoSil N=36 n (%)	Comparator N=9 n (%)	Total N=45 n (%)
Thrombotic and embolic events	**2 (5.6)**	**0**	**2 (4.4)**
SAEs	2 (5.6)	0	2 (4.4)
Postoperative bleeding at surgical site	**16 (44.4)**	**3 (33.3)**	**19 (42.2)**
SAEs	5 (13.9)	0	5 (11.1)
Immunological events	**4 (11.1)**	**1 (11.1)**	**5 (11.1)**
SAEs	1 (2.8)	0	1 (2.2)
Abscess and other surgical related infections	**2 (5.6)**	**3 (33.3)**	**5 (11.1)**
SAEs	0	1 (11.1)	1 (2.2)
Tissue adhesions	**8 (22.2)**	**2 (22.2)**	**10 (22.2)**
SAEs	4 (11.1)	1 (11.1)	5 (11.1)

More thrombotic/embolic events and postoperative bleedings were seen in the TachoSil-group. Tissue adhesions were similar.

Immunogenicity testing and viral serology was not performed in paediatric subjects up to 6 months of age, nor for subjects enrolled in the paediatric extension part. Immunogenicity was tested in 2 children treated with TachoSil and 2 children treated with Surgicel. Only 1 paediatric subject had a 1-month follow-up test, which was negative for antibodies.

Immunological adverse events:

Table 4: Subjects with ESIs by preferred term and treatment (paediatric study pool)

Medical Category PT	TachoSil N=36 n (%)	Comparator N=9 n (%)	Total N=45 n (%)
Immunological events	**4 (11.1)**	**1 (11.1)**	**5 (11.1)**
Hypotension	2 (5.6)	0	2 (4.4)
Blood pressure decreased	1 (2.8)	0	1 (2.2)
Drug hypersensitivity	1 (2.8)	0	1 (2.2)
Oedema	1 (2.8)	0	1 (2.2)
Pruritus	1 (2.8)	0	1 (2.2)
Respiratory distress	1 (2.8)	0	1 (2.2)
Wheezing	1 (2.8)	0	1 (2.2)
Rash	0	1 (11.1)	1 (2.2)

Immunological events in the TachoSil population cover a broad spectrum of clinical symptoms – including respiratory symptoms, cardiovascular, and named drug hypersensitivity. On the comparator side, 1 subject was reported with a rash – considered to be a multi-causal symptom.

Two fatal outcomes after TachoSil treatment were submitted as follows:

(1) A 3-year-old boy treated with TachoSil in Study TC-019-IN had a fatal event of multi-organ failure that began on Day of Surgery and ended 62 days post-dose and was considered not related to study treatment by the investigator. The subject had concurrent metabolic acidosis, decrease haemoglobin, decrease sodium, decrease potassium, ascites, renal dysfunction, thrombocytopenia, pleural effusion, abdominal bleeding, disseminating intravascular coagulopathy (DIC), respiratory distress, and sepsis.

(2) A 6-month-old girl treated with TachoSil in Study TC-2402-040-SP had a fatal event of exsanguination that began and ended 42 days post-dose and was considered not related to study treatment by the investigator. The subject had a concurrent illness of end stage renal disease and hyperoxaluria as well as concurrent adverse events of hepatic necrosis, portal vein thrombosis, septic shock, disseminated intravascular coagulation, *Stenotrophomonas* infection, *Enterobacter* infection, *Mycobacterium* abscess infection, anastomotic complication, and splenic rupture.

Discontinuation due to adverse events

In the paediatric study pool, 6 subjects discontinued the study: 4 out of 35 subjects in the TachoSil- and 2 out of 9 subjects in the Comparator-group. 4 subjects (2 in each group) were lost to follow-up or had "other" reasons for discontinuation. 2 subjects from the TachoSil group discontinued due to death or Adverse event.

Post marketing experience

The MAH provided an estimation on 10.2 million patients treated with TachoSil in the post-marketing setting.

Table 5	**Patient exposure for TachoSil from marketing experience by region**	
Region	**Cumulative patients since January 2007(a)**	**Cumulative patients since launch(b)**
European Union	6,369,421	N/A
Asia	239	N/A
Japan	983,399	N/A
*Rest of World (ROW)	2,119,419	N/A
USA	209,195	N/A
Total	**9,681,673**	**10,168,133**

*For Japan, Iceland, Saudi Arabia and Montenegro (ROW) the sales data has been taken from the partner.

1. Shipment data covers the period from January 2007 to May 2021.
2. Shipment data covers the period from June 2004 to May 2021. Cumulative historical data was not broken down by region. N/A- Not available.

Up to 08 June 2021, a total of 1,283 spontaneously worldwide reported adverse drug reactions (ADRs) have been received; 556 ADRs were considered serious, and 713 ADRs were considered non serious. The review of post-marketing cumulative data revealed no new safety concerns and no amendments of the product labelling for safety are considered necessary at this time.

Bibliographic data:

One article (Ekici et al) is considered to be of special interest regarding safety: The article described a 3 year-old girl presenting with spinal cord "tumour". From her medical history it was learned that she was operated on cervical meningocele during her neonatal period with use of TachoComb due to CerebroSpinal Fluid (CSF) leakage. At the age of 3 years a "tumour" was removed. Histologically the whole mass constituted a foreign body reaction against TachoComb for dural repair.

2.5.1. Discussion on clinical safety

Beyond the safety-analyses from the preceding procedures, pooled safety-analyses have been presented.

Safety-data were pooled from both above described studies. Overall numbers are low (36 TachoSil-, and 9 Surgicel-treated subjects), and results are difficult to interpret due to various confounding factors. Most of the patients were enrolled open-label. Comparative design applies only for 8 TachoSil-treated subjects.

SAEs were reported by 17 of 34 subjects in the TachoSil group and 4 of 9 subjects in the Comparator group. No subject in either treatment group experienced an SAE that was considered related to study treatment.

Evaluation of ESIs revealed more thrombotic/embolic events and postoperative bleedings in the TachoSil-group. Tissue adhesions were similar for TachoSil and Comparator. However, no conclusions should be drawn from such low numbers. Two fatal case-reports concern the TachoSil group – both outcomes not related with the TachoSil treatment.

Immunogenicity testing was not done sufficiently. Pattern of adverse events on potential immunological/ allergic reactions seem to be in favour of Surgicel. However, all events were reported for single patients, only – precluding valid comparisons.

Low patient numbers in age-group-related subgroup-analyses similarly are considered to be challenging and do not allow valid conclusions. Of note, TachoSil patient-group covers the age of 0-13 years – bearing a gap from 13 to 18 years to the adult studies. As this adolescent age-group represents a phase of significant growth and maturation of organs and body-systems, this gap is considered to be relevant.

In summary, safety evaluation of clinical-study-data does not allow valid conclusions, mainly due to low patient numbers.

Bibliographic data:

The article (Ekici et al) described a 3 year-old girl presenting with spinal cord "tumour". From her medical history it was learned that she was operated on cervical meningocele during her neonatal period with use of TachoComb due to CerebroSpinal Fluid (CSF) leakage. At the age of 3 years a "tumour" was removed. Histologically the whole mass constituted a foreign body reaction against TachoComb for dural repair. The causative collagen-sponge in TachoComb is the same as in TachoSil, and the described reaction is at least clinically plausible. Therefore, the following statement has been added in section 4.8 of the SmPC: "Some cases of product residue, that might have caused a foreign-body reaction in the form of granuloma, have been reported."

In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation study is warranted and the company is asked to submit a variation to update the RMP strictly according to the latest EU-RMP template, including part V.3, and to include a cat. 3 PASS protocol, by August 2023.

2.5.2. Conclusions on clinical safety

Based on the safety data provided, the paediatric extension of indication can be recommended in the following indication: TachoSil is indicated in adults and children from 1 month of age 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.

It was agreed not to recommend the paedaitric extension of indication for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery.

A bibliographical case-report on histologically proven foreign-body-reaction-granuloma 3 years after dura-repair raises concern. Therefore, the following statement warning has been added in section 4.8 of the SmPC: "Some cases of product residue, that might have caused a foreign-body reaction in the form of granuloma, have been reported."

In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation study is warranted and the company is asked to submit a variation to update the RMP strictly according to the latest EU-RMP template, including part V.3, and to include a cat. 3 PASS protocol, by August 2023.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 9.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Thrombotic and embolic events • Immunological events including hypersensitivity • Gastrointestinal obstruction
Important potential risks	• Transmission of infectious agents •
Missing information	• Lack of experience in gastrointestinal anastomosis surgery • Lack of experience in pregnant or lactating women • Repeated use of TachoSil • Use in paediatric population

Pharmacovigilance plan

In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation study is warranted and the company is asked to submit a variation to update the RMP strictly according to the latest EU-RMP template, including part V.3, and to include a cat. 3 PASS protocol, by August 2023.

Risk minimisation measures

Important identified risk

Safety concern	Routine risk minimisation activities
Thrombotic and embolic events	Routine risk communication: • SmPC Sec. 4.2, 4.3, 4.4, 4.8 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • The surgeons should use TachoSil only for epilesional use only. • TachoSil must not be used intravascularly by surgeons.

Safety concern	Routine risk minimisation activities
Immunological events including hypersensitivity	Routine risk communication: • SmPC Sec. 4.2, 4.3, 4.4, 4.8 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • Patients with known hypersensitivity to the active substance or to any of the excipients must not be administered TachoSil • Recommendation of discontinue TachoSil in patients with hypersensitivity symptoms occur • Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Safety concern	Routine risk minimisation activities
Gastrointestinal obstruction	Routine risk communication: • SmPC Sec. 4.2, 4.4. 4.8, 6.6 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • Surgeons should be aware that events of adhesions to gastrointestinal tissues leading to gastrointestinal obstruction have been reported with use in abdominal surgery carried out in proximity to the bowel • Recommendation for surgeons to ensure tissue areas outside the desired application area are adequately cleansed before administration of TachoSil, to prevent the development of tissue adhesions at undesired sites

Important potential risk

Safety concern	Routine risk minimisation activities
Transmission of infectious agents	Routine risk communication: • SmPC Sec. 4.4, 6.6 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • Physicians should be aware that when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded • Recommendation of recording the name of the patient and batch number of the product in order to maintain a link between the patient and the batch of the product. • Recommendation that TachoSil should be used under sterile conditions. Prior to application the wound area should be cleansed, e.g., from blood, disinfectants, and other fluids.

Missing information

Lack of experience in gastrointestinal anastomosis surgery	Routine risk communication: • SmPC Sec. 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • The treating surgeons should be aware that insufficient data have been obtained on the use of this product in gastrointestinal anastomoses surgery.
Lack of experience in pregnant or lactating women	Routine risk communication: • SmPC Sec. 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • The treating surgeons should be aware that the safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials • TachoSil should be administered to pregnant and breastfeeding women only if clearly needed.
Repeated use of TachoSil	Routine risk communication: • SmPC Sec. 4.8 • PL Sec. 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• The use of TachoSil is restricted to experienced surgeons • The treating surgeons should be aware that allergic reactions may occur especially if TachoSil is used repeatedly.
Use in paediatric population	Routine risk communication: • SmPC Sec. 4.2,5.1 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The use of TachoSil is restricted to experienced surgeons • The treating surgeons should be aware that insufficient data have been obtained on the use of this product in children aged 0 to 18 years and that no recommendation on a posology can be made.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH included editorial changes to the product information which are acceptable.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH has applied for the following paediatric indication: "TachoSil is indicated in adults and children aged 1month to 18 years for supportive treatment in surgery, for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery (see section 5.1)."

3.1.2. Available therapies and unmet medical need

At present, none of the centrally approved fibrin sealants has yet received an authorisation for patients <18 years of age.

3.1.3. Main clinical studies

No new study-results have been submitted. Previously submitted data include results from clinical studies TC-019-IN and TC-2402-040-SP. Bibliographical data have also been provided as well as an extrapolation exercise.

3.1.4. Favourable effects

Efficacy is mainly based on the extrapolation exercise. TachoSil patch is a locally applied medicinal product and the amount of the patch required to be applied should be adequate to the wound size and underlying clinical need for the patient, no exposure effect is expected to affect the outcome of a treatment. Although, patients' weight and wound size will likely to be different between populations, exposure-response relationship is not expected to differ due to local modality of application, and adjustment the size of a patch to wound size and bleeding rate.

The apparently substantial differences in haemostasis physiology with pronounced numerical differences in plasma levels of most haemostatic proteins and functional readouts provide sound justification for an exclusion of neonates (i.e. children up to 1 month of age) from the requested paediatric extension of indication.

Secondly, it is noted that the question of the exact age at which the coagulation system can be regarded fully established cannot be answered conclusively. However, current literature supports the notion of most pronounced changes towards adult values within the first month of life and indicates a trend of stabilisation beyond the 1-month boundary. Moreover, TachoSil's composition and its mechanism of action argue for a rather minor impact of the patient's own haemostatic system and the few remaining potentially relevant aspects of development are not considered likely to exert any significant age-related impact beyond the first month of life.

3.1. Uncertainties and limitations about favourable effects

The submitted data do not provide an appropriate evidence base for serving as a stand-alone paediatric development. Both available clinical studies (TC-019-IN, TC-2402-040-SP) rely on a narrow patient population. Provided clinical-study data have been submitted in previous procedures (FUM and Article 46) and reveal challenging results due to a severely ill patent collective (TC-019-IN) and low patient numbers. From a biostatistics point of view, for both studies, confidence intervals for the primary efficacy endpoint were very wide, and hence the uncertainty large. Regarding the pooled data, due to post-hoc nature and heterogeneity of the trial-designs, results are even more subject to uncertainty.

Moreover, clinical study data are limited to a paediatric age-range of 0-13 years leaving a relevant gap in knowledge with regard to the treatment of adolescents, which due to significant growth and maturation of organs and body-systems may represent a particularly challenging age-group.

The presented bibliographic data reflect a heterogeneous collection, not clearly targeting the approved clinical use of TachoSil. No robust efficacy-data are reflected in these reports. Although individual positive statements regarding efficacy are found in several publications, these data cannot replace convincing clinical-study-results.

3.1. Unfavourable effects

A published case-report on a clinically relevant cervical tumour formation (i.e. a histologically proven foreign-body granuloma) in a 3-year-old child that had been treated with TachoSil for dura repair led to

the identification of multiple post-marketing reports of incomplete bio-resorption and foreign-body granuloma formation upon TachoSil treatment. Even though the majority of these reports concerned adults and cases were apparently not limited to neurosurgical procedures, the only limited amount of available data precludes drawing conclusions with regard to potential impacts of patient age and / or therapeutic indication. However, the risk of granuloma formation is considered particularly relevant in the context of anatomically confined spaces (e.g. neurosurgery) and the immunological basis of this foreign-body reaction may suggest a possible impact of patient age. Given its potential clinical relevance and the clear relationship to an incomplete bio-resorption of TachoSil material, foreign-body granuloma formation has been added as an identified risk of TachoSil treatment and hence a statement has been included in section 4.8 of the SmPC.

3.1. Uncertainties and limitations about unfavourable effects

Pooled safety-data from both above described studies cover 36 TachoSil- and 9 Comparator- (Surgicel-) treated subjects. However, data-pool is considered to be narrow and heterogeneous. No valid information is available on immunogenicity. However, no specific additional risk has been identified.

In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation study is warranted and the company is asked to submit a variation to update the RMP strictly according to the latest EU-RMP template, including part V.3, and to include a cat. 3 PASS protocol, by August 2023.

3.2. Benefit-risk assessment and discussion

3.2.1. Balance of benefits and risks

The MAH performed a paediatric extrapolation exercise which provided additional support for i) the expectation of an age-independent pharmacological (i.e. haemostatic) activity of TachoSil beyond the first month of life and ii) an age-independent treatment effect in the context of hepatic resection.

However, particularly due to remaining concerns with regard to its use for dura repair in neurosurgery, the presented evidence base was not considered appropriate to justify a paediatric extension across the entire spectrum of currently approved indications in adults, as originally proposed by the MAH.

A paediatric extension of indication from 1 month of age, restricted to the product's use for tissue sealing and vascular surgery (i.e. excluding its use for dura mater repair in neurosurgery) has been considered acceptable.

Foreign-body granuloma formation has been added as an identified risk of TachoSil treatment and hence a statement has been included in section 4.8 of the SmPC. In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation study is warranted and the company is asked to submit a variation to update the RMP strictly according to the latest EU-RMP template, including part V.3, and to include a cat. 3 PASS protocol, by August 2023.

3.2.2. Additional considerations on the benefit-risk balance

Not applicable.

3.3. Conclusions

The overall B/R of TachoSil is positive for this paediatric extension of indication 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.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of children aged 1 month to 18 years 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, based on available bibliographical data, results from study TC-2402-040-SP which compared TachoSil with Surgicel Original as adjunct to primary surgical treatment in both adult and paediatric subjects, and results from Study TC-019-IN; a prospective, uncontrolled study in paediatric subjects. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the product information. Version 9.0 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important

(pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'TachoSil-H-C-505-II-117'

Attachments

1. SmPC, Package Leaflet (changes highlighted)

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 10 March 2023. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 10 March 2023. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.