EU Risk Management Plan for TachoSil (Human Fibrinogen, Human Thrombin)

RMP version to be assessed as part of this application:

RMP Version number: 9.3

Rationale for submitting this RMP:

-Update of the RMP following the recommendation from EMA, as a Response to Request for Supplementary Information issued on 08 Feb 2024 by PRAC Rapporteur, on the submitted type II variation

Data lock point for this RMP: 08-Jun-2023

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QPPV name: Ioana Frent

QPPV signature:

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Abbreviations

DLP	Data Lock Point
EMA	European Medicines Agency
HAs	Haemostatic agents
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
PBRER	Periodic Benefit Risk Evaluation Report
PASS	Post Authorisation Safety Study
PL	Patient Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Human Fibrinogen Human Thrombin
Pharmacotherapeutic group(s) (ATC Code)	ATC code: B02BC30 Pharmacotherapeutic group: Local haemostatics
Marketing Authorisation Holder	Corza Medical GmbH
Medicinal products to which this RMP refers	TachoSil sealant matrix.
Invented name(s) in the European Economic Area (EEA)	TachoSil
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: TachoSil is a local haemostatic that contains fibrinogen and thrombin as a dried coating on the surface of a collagen matrix.
	Summary of mode of action: The mechanism of action of TachoSil follows the principles of physiological fibrin clot formation. TachoSil, in contact with physiological fluids, e.g. blood, lymph or physiological saline solution their components of the coating dissolve and partly diffuse into the wound surface. This is followed by the fibrinogen-thrombin reaction which initiates the last phase of physiological blood coagulation. Fibrinogen is converted into fibrin monomers which spontaneously polymerise to a fibrin clot, which holds the collagen matrix tightly to the wound surface. The fibrin is then cross linked by endogenous factor XIII, creating a firm, mechanically stable network with good adhesive properties and therefore provides sealing as well.
	Important information about its composition: TachoSil is a sealant matrix that contains human fibrinogen, human thrombin and equine collagen
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labelling and Package Leaflet

Indication(s) in the EEA	Current: 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.
	Proposed: N/A
Dosage in the EEA	The use of TachoSil is restricted to experienced surgeons. The quantity of TachoSil to be applied should always be oriented towards the underlying clinical need for the patient. The quantity of TachoSil to be applied is governed by the size of the wound area. Application of TachoSil must be individualised by the treating surgeon. In clinical studies, the individual doses have typically ranged from 1-3 units (9.5 cm x 4.8 cm); application of up to 10 units has been reported. For smaller wounds, e.g. in minimally invasive surgery the smaller size matrices (4.8 cm x 4.8 cm or 3.0 cm x 2.5 cm) or the pre-rolled matrix (based on a matrix of 4.8 cm x 4.8 cm) is recommended.
Pharmaceutical form(s) and strengths	TachoSil is a medicated patch containing human fibrinogen 5.5 mg and human thrombin 2.0 IU per cm2. It is available in three sizes: 9.5 cm x 4.8 cm, 4.8 cm x 4.8 cm and 3.0 cm x 2.5 cm.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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.

TachoSil is indicated in adults for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery

Incidence and Prevalence:

Globally, there are an estimated 234.2 million major surgical procedures (mean surgical rate, 4016 per 100,000 population) performed worldwide every year [1].

Based on national data from England, there were an estimated 157,046 (of 6.491million) 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 national hospital survey data in the US, there were approximately 14 million hospitalizations involving surgery in 2006 [2,3].

Vascular Surgery: 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 [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) [5-7]. In the US, based upon data from the National Hospital Discharge Survey, the estimated number of common vascular procedures performed in 2000 was 801,537 (234 per 100,000 population) [8].

Demographics of the population:

The demographic profile varies enormously by operation. Based on English national figures [8], the population for whom TachoSil use is projected may have an overall average age of 50 years and a male : female sex ratio of 0.47 : 0.53. Based upon US national survey data, among patients undergoing inpatient surgical procedures in 2006, mean age was 50.1 years and a slight majority of patients were female (54.3%) [2].

The main existing treatment options:

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 (≈30) 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 [9].

To maximise haemostasis and to reduce the rate of postoperative haemorrhagic events, a wide variety of HAs have been used. Some of the available products include thrombin sealant, fibrin glue, oxidized methylcellulose, and gelatine matrix. Each of these agents differs in mechanism of action and application [9].

Several locally acting hemostatic agents have been developed for the management of hemostasis and various products may potentially be used in certain operative settings. In a prospective study assessing the use of local hemostatic agents in patients in France undergoing partial nephrectomy, hemostasis management involving the use of a second-line hemostatic agent occurred among approximately 8.2% of patients [9]. Moreover, approximately 5.0% of patients receiving hemostatic agents were transfused perioperatively.

Natural history of the indicated condition in the population, including mortality and morbidity:

Extrapolation from population-based regional data from England [10], there were a predicted 4.8 million deaths which occurred after surgery in the EU in 2005. Inpatient 30-day mortality among patients in the US undergoing inpatient surgical procedures in 2006 was estimated at 1.32% [2].

Important co-morbidities:

Although risks factors vary enormously by operation type, age is an important factor, as is co-morbidity. Post-operative bleeding is a cause of prolonged hospital stay[11].

No overall figures for important co-morbidities in the target population can be provided or would be appropriate as the co-morbidities vary greatly and are highly dependent on the case mix.

Part II: Module SII - Non-clinical part of the safety specification

The nonclinical investigation of TachoSil, addressing pharmacodynamics, pharmacokinetics and toxicity, include studies with TachoSil itself (also as pre-rolled TachoSil) and studies with its 2 predecessors, namely TachoComb and TachoComb H. Both predecessor products contain bovine components, ie, bovine thrombin (TachoComb) and bovine aprotinin (TachoComb and TachoComb H). TachoSil was developed in order to omit these bovine components and thus to prevent any risk of transmittance of bovine diseases to humans; bovine thrombin was substituted with human thrombin, while bovine aprotinin was omitted completely. Nonclinical studies have demonstrated that aprotinin (a protease inhibitor that inhibits the fibrinolytic enzyme plasmin and that was originally intended to delay biodegradation of the hemostatic patch) is dispensable for the hemostatic efficacy of TachoSil. The feasibility of the above bridging concept was verified by several nonclinical studies, which have shown comparability between TachoSil and its predecessors in terms of pharmacodynamic properties, pharmacokinetic behavior and toxicological potential.

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity use

- Key issues identified from acute or repeat-dose toxicity studies

Single-dose toxicity

Following single intraperitoneal (ip) administration onto a wound surface in minipigs, data indicate a very good safety profile of TachoSil even at doses of about 28-fold higher than those indicated for use in humans (2 patches/ 70 kg patient; 21 mg/kg). Local reactions to the implants (granulation tissue, cell accumulation) reflect the ongoing biodegradation and are considered to be a non-toxic response. These data are supported by single-dose toxicity studies using TachoComb and TachoComb H in rats, dogs and minipigs after single ip administration (onto wounds or into abdominal cavity), showing a very good safety profile at doses of 2.3-fold (minipigs), 24-fold (dog) and 48-fold (rat) higher than those indicated for use in humans (ie, an average of 2 patches per surgical procedure).

Repeat-dose toxicity

The no-observed-adverse-effect-level (NOAEL) for TachoSil in the minipig, following repeated administration, was 79.1 mg/kg, which is about 4-fold higher than the dose indicated for use in humans (ie, an average of 2 patches per surgical procedure/ 70 kg patient; 21 mg/kg). A supportive 4-week repeat-dose toxicity study was conducted with TachoComb in rats. The surgical patch (0, 13, 131 or 1044 mg/kg) was inserted into the abdominal cavity by laparotomy once weekly for a total of 4 doses, followed by an autopsy 1 or 4 weeks after the last administration. In the 131 mg/kg group, there were no substantial changes.
Observed adhesions of the surgical patches to abdominal organs and the mesentery were expected and do not represent evidence of toxicity. At the 1044 mg/kg dose level, there were slight transient decreases in body weight gain and food and water intake during treatment. Hematological investigations revealed a statistically significant, slight to moderate increase in differential neutrophil count and a decrease in differential lymphocyte count at the end of the treatment period. These effects were reversible and are interpreted as a result of the surgical procedure and the large amount of patches administered ip, rather than signs of toxicity caused by exaggerated pharmacology. Similar to the 131 mg/kg group, gross pathology revealed adhesions of the surgical patches to abdominal organs and the mesentery.
Overall, the observed findings were reversible and considered to be the physiological response to surgical

intervention and biodegradation of the patch. The NOAEL is defined at 131 mg/kg because, unlike the findings observed in the 1044 mg/kg dose group, there were no significant changes in the differential neutrophil and lymphocyte count, despite the ongoing repair processes as indicated by the histopathologica findings.

- Reproductive/developmental toxicity

According to ICH Guideline S6 (1997) [1], the need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication, and intended patient population. In view of this, there is no rationale for the conduct of reproductive toxicity studies for collagen patches containing heterologous proteins from equine (collagen) and human (fibrinogen, thrombin) sources, especially considering that TachoSil is a drug product intended to be used topically during surgical intervention, usually applied only once per patient. Moreover, considering the recommended and common study designs for the different types of reproduction toxicity studies, it does not appear feasible to administer TachoSil surgical patches to animals by the intended route of administration used in humans. Therefore, no reproductive/developmental toxicity studies were performed.

- Genotoxicity

Genotoxicity studies have not been conducted. According to ICH Guideline S6 (1997), genotoxicity studies conducted with products that consist of large quantities of proteins may yield uninterpretable results. It is not expected that these substances would interact directly with DNA or other chromosomal material. Thus, there is no clear rationale for the conduct of genotoxicity studies for topically administered collagen patches containing proteins from equine (collagen) and human (fibrinogen, thrombin) sources. Therefore, no genotoxicity studies were conducted

- Carcinogenicity:

Carcinogenicity studies have not been conducted (According to ICH Guideline S1A (1995) and ICH Guideline S6 (1997), there is no rationale for the conduct of carcinogenicity studies with TachoSil based on the mode and number of administrations (topical administration during surgical intervention, usually once per patient) and its compositionm(heterologous proteins for animals).

Safety pharmacology

Local tolerance
The local tolerance of TachoSil was assessed, as part of toxicity studies, in minipigs after 1, 3, 6 and 12 months, following repeated- or single administration, onto liver and/or spleen wounds.
The results of all studies confirmed the good local tolerance of TachoSil, also as a pre-rolled patch. In addition, data showed comparable good local tolerance of the predecessors TachoComb and TachoComb H. This is true for different organs and tissues (brain, liver, spleen) in all animals tested (rabbits, dogs, pigs). Local reactions to the implants (cellular accumulation, granulation tissue) reflect the ongoing repair and biodegradation process and are considered to be a non-toxic response. In a few studies, adhesions were observed, which were associated with granulation tissue. In experimental settings, in which the surgical patches were administered intraperitoneally (ie, not covering a wound surface), this is an expected finding as the active side of the patches (coated with thrombin and fibrinogen) was free to form a fibrin clot which adhered the patch to surrounding tissue and organs. In cases where the patches were applied to a wound surface, adhesions were either not observed or occurred to a similar extent in sham-operated animals, showing that these adhesions were related to the technical procedure of the laparotomy and subsequent wound healing. Therefore, adhesions observed after application of surgical patches to wound surfaces are not considered to be of toxicological significance.

Recently a 12 month animal study investigating the biodegradation of TachoSil in liver resection has been Finalized. The results show that both the fibrin clot formed from the TachoSil coating and the equine collagen sponge shrink and become encapsulated by granulation tissue during the process of degradation. While some animals showed complete degradation of TachoSil 12 months after its administration to a liver wound, remnants were still observed in others. No evidence of local intolerability was observed.

Antigenicity of equine collagen
Since TachoSil is composed of equine collagen, the antigenic potential of equine collagen was investigated in different experimental settings by using either TachoSil or TachoComb or its single components.
Several of the studies identified human fibrinogen to be highly immunogenic in the guinea pig and rat. This is confirmed by results from a repeat-dose toxicity study with TachoSil in minipigs where high titers of antibodies against human fibrinogen were detected in all animals. Nevertheless, it is assumed that both human fibrinogen and human thrombin as homologous proteins are not antigenic in humans.

Antigenicity due to gamma-irradiation
To rule out the formation of neoepitopes caused by gamma irradiation of TachoSil (the final sterilization process of the patch) a study was performed in rats to investigate the immunogenic potential of irradiated compared to non-irradiated single components of TachoSil (human fibrinogen, human thrombin, equine collagen) and TachoComb (human fibrinogen, bovine thrombin, bovine aprotinin, equine collagen). In the rat, an immune response was elicited only with human fibrinogen and human thrombin, both heterologous proteins for the rat. Furthermore, the data showed no evidence of neoepitope formation of any of the single components of TachoSil due to gamma irradiation.

Viral safety
The viral safety of TachoSil is assured by appropriate blood donor screening, plasma testing and appropriate inactivation steps during the manufacturing processes.

Safety of excipients
The safety and tolerability of the excipient of TachoSil, namely the non-coated collagen patch (also referred to as Tachotop), was investigated in singledose toxicity studies in rats and minipigs. The noncoated collagen patch was well tolerated and degraded in a dose-dependent manner over time.

Summary of non-clinical part of the safety specification

Single dose toxicity studies in different species of animals have shown no signs of acute toxic effect.
Since human fibrinogen and human thrombin are heterologous to the minipig, the formation in this species is not predictive of an immunogenic response in humans (ICH Guideline S6, 1997) [12].
The overall weight of evidence taking into account published data and results from non-clinical and clinical studies with TachoSil or predecessor products leads to the conclusion that the carcinogenic risk of TachoSil and its components is negligible.
Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development. Therefore, TachoSil should be administered to pregnant and breastfeeding women only if clearly needed. No evidence of local intolerability has been observed in animal studies.
It is not expected that TachoSil would interact directly with DNA or other chromosomal material.

The preclinical safety studies revealed no safety concerns relevant to the intended use of TachoSil. No additional non-clinical data are considered necessary for special populations.

Part II: Module SIII - Clinical trial exposure

Brief overview of development

The clinical development of TachoSil has extended over a period of 14 years starting in 2000. In the pooled and unpooled studies in the Integrated Summary of Safety (ISS) data base, 4175 adult subjects and 36 paediatric subjects were exposed to TachoSil. The development program encompassed the following studies [13]:

1. An initial series of 3 studies (TC-013-IN, TC-014-IN, and TC-015-IN) in 3 surgical applications (lung lobectomy, liver resection, and kidney resection).
2. The addition of a second liver resection study (TC-016-IN).
3. European Union (EU) post-authorisation commitment (TC-018-IN) evaluating potential safety concerns.
4. EU post-authorisation commitment (TC-019-IN) evaluating paediatric use when undergoing hepatic surgery.
5. Studies further expanding the clinical evidence for TachoSil (TC-021-IM and TC-023-IM) conducted in subjects undergoing lung and cardiovascular surgery, respectively.
6. A study in hepatic surgery in adults and children (TC-2402-040-SP).
7. A study as suture line sealing in dura mater closure (TC-2402-038-SP).

All Study Pool

Table SIII.1: Exposure By Dose

Dose of Exposure (Number of patches*)	N (%)
≤1☐	551 (55.3)
>1 - 2	289 (29.0)
>2 - 3	90 (9.0)
>3 - 4	38 (3.8)
>4	25 (2.5)
Missing	4 (0.4)
Median	1
Min-Max	0.25 - 10
Total	997

* Large patches (9.5 cm x 4.8 cm x 0.5 cm) were used in the TachoSil studies, except in study TC-2402-038-SP,
in which both large and medium (4.8 cm x 4.8 cm x 0.5 cm) patches were allowed.

Note: The all study pool includes the following studies: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM, TC-023-IM, TC-2402-038-SP and TC-2402-040-SP.

Table SIII.2 Exposure By Age Group and Gender

Age Group	Persons	
	Male – N (%)	Female – N (%)
18 - 65	331 (62.2)	340 (73.1)
66-75	162 (30.5)	100 (21.5)
>75	39 (7.3)	25 (5.4)
Total	532	465

Note: The all study pool includes the following studies: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN,
TC-021-IM, TC-023-IM, TC-2402-038-SP and TC-2402-040-SP.

Table SIII.3 Exposure By Ethnic or Racial Origin

Ethnic/Racial Origin	Persons – N (%)
Caucasian	970 (97.3)
Non-Caucasian	27 (2.7)
Total	997

Note: The all study pool includes the following studies: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN,
TC-021-IM, TC-023-IM, TC-2402-038-SP and TC-2402-040-SP.

Pediatric Study Pool

Table SIII.4 Exposure By Dose

Dose of Exposure (Number of	N (%)
≤1☐	25 (69.4)
>1 - 2	8 (22.2)
>2 - 3	2 (5.6)
>3 - 4	1 (2.8)
Median	1
Min-Max	0.25 - 4

Total	36

* Only large patches (9.5 cm x 4.8 cm) were used in clinical studies.
Note: The pediatric study pool includes the following studies: TC-019-IN and TC-2402-040-SP (pediatric subjects).

Table SIII.5 Exposure By Age Group

Age Group	Persons - N (%)
10-23 Months	20 (55.6)
2-11 Years	12 (33.3)
12-16 Years	4 (11.1)
Total	36

Note: The pediatric study pool includes the following studies: TC-019-IN and TC-2402-040-SP (pediatric
subjects).

Table SIII.6 Exposure By Ethnic or Racial Origin

Ethnic/Racial Origin	Persons
Caucasian	29 (80.6)
Non-Caucasian	7 (19.4)
Total	36

Note: The pediatric study pool includes the following studies: TC-019-IN and TC-2402-040-SP (pediatric
subjects).

Special Populations

Patients were included in the clinical trials and exposed to TachoSil on the basis of a specific surgical condition and according to the scope of the respective trial protocol, not selected by demographic or other characteristics.

TachoSil is a single use product that degrades in the body after use, therefore duration of exposure and person-years of exposure are not considered clinically relevant.

TachoSil is not recommended for systemic administration and is not absorbed in the circulation; special groups such as pregnant women, lactating women, patients with renal impairment, liver impairment and cardiac impairment are not applicable to a product like TachoSil and no data are available.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 LIMITATIONS OF ADVERSE DRUG REACTION DETECTION COMMON TO CLINICAL TRIAL DEVELOPMENT PROGRAMS

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	997 patients were exposed to TachoSil in the controlled clinical trials over the whole clinical trial program.	With an exposed clinical study population of 997 subjects, ADRs with a frequency of ≥1 in 332 could be reasonably excluded. Therefore, any ADRs with a frequency of <1 in 332 will likely not have been detected. ADRs are generally as expected from the specific surgical procedures or related to the underlying disease condition.
Due to prolonged exposure	Not applicable to TachoSil as it is one time application.	
Due to cumulative effects	Not applicable to TachoSil as it is one time application.	
Which have a long latency	Two of the clinical trials (dura sealing and hepatic resection) included 6 months of follow up. Fifteen of the 27 seroconverted subjects from the hepatic study were followed up for 24 months for antibody titer and immune- mediated adverse events.	The data analyzed from the 6-month Study Pool (2 clinical trials) did not show any differences in safety profile of the TachoSil vs. Comparator group. The pattern of TEAE, SAEs and adverse events of special interest did not show any trends. None of the seroconverted subjects reported adverse events that could be attributed to development of antibodies. The antibodies to equine collagen did not show cross reactivity to human collagen. One patient with fibrinogen antibodies had confounding factor (packed cell transfusion 2 weeks after the surgery where TachoSil was used). This subject did not have any bleeding, bruising or other adverse events and all coagulation tests were within normal ranges at the 26 week visit.

SIV.2 EFFECT OF EXCLUSION CRITERIA IN THE CLINICAL TRIAL DEVELOPMENT PLAN

Exclusion Criteria That Will Remain as Contraindications

Criteria	Implications for Target Population
Hypersensitivity to the active substances or to any of the excipients.	Patients who have hypersensitivity to human fibrinogen or human thrombin or any of the excipients in TachoSil should not be treated with TachoSil. An alternate treatment should be administered.

Exclusion Criteria That are NOT Proposed to Remain as Contraindications

Criteria	Reason for Being an Exclusion Criterion	Justification for Not Being a Contraindication
Pregnant women	Ethical consideration	Animal reproduction studies have not been conducted with TachoSil. There are no adequate and well- controlled studies in pregnant women. It is also not known whether TachoSil can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The SmPC section 4.6 states that TachoSil should be administered to pregnant and breastfeeding women only if clearly needed.
Breastfeeding women	Ethical consideration	It is not known whether the components of TachoSil are excreted in human milk. The SmPC section 4.6 states that TachoSil should be administered to pregnant and breastfeeding women only if clearly needed.

Children and adolescents less than 18 years of age.	To prevent exposure to a vulnerable population prior to establishing efficacy and safety of TachoSil in the adult population.	As a part of a post-authorization commitment, Takeda performed a prospective single arm intervention study on the efficacy and safety of TachoSil in children undergoing liver surgery (study TC-019-IN). The results of this study were submitted to the EMEA 15 May 2008. Sixteen children were included in the trial. Median (range) age was 15 (2.5 -147.5) months. The study showed TachoSil to be effective in obtaining intra-operative hemostasis in the majority of children undergoing liver resection with or without segmental liver transplantation. Furthermore it can be concluded from the safety data collected that TachoSil was not considered to be related to any of the AEs/SAEs reported.

Exclusion Criteria That are NOT Proposed to Remain as Contraindications

Criteria	Reason for Being an Exclusion Criterion	Justification for Not Being a Contraindication
		Also a randomized, open-label, controlled, parallel-group, multi-center therapeutic confirmatory trial comparing TachoSil with Surgicel Original for the secondary treatment of local hemorrhage from the hepatic resection wound in adult and pediatric patients was conducted (study TC-2402-040-SP). Twenty pediatric subjects, from 3 months to 13 years of age, received TachoSil during the study. The results were generally similar across the pediatric age groups and similar to the adults data from study TC-2402-040-SP (although data for the adolescent group were limited). Thus TachoSil has demonstrated an acceptable safety profile and is clinically appropriate for use in pediatric patients.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Patients were included in the clinical trials and exposed to TachoSil on the basis of a specific surgical condition and according to the scope of the respective trial protocol, not selected by demographic or other characteristics. TachoSil was used in all trials as an additional therapeutic measure after primary closure of the wound had been applied according to the standard practice. Patients were under general anesthesia at the time of TachoSil application. Duration of exposure, person-years of exposure and special groups such as pregnant women, lactating women, renal impairment, liver impairment and cardiac impairment are not clinically relevant for a product like TachoSil with only local application and no data are available.

Children

Takeda, the previous MAH has completed the TC-2402-040-SP liver trial in adult and pediatric patients and the clinical study report has been finalized. The results for the pediatric patients indicated that the proportion of pediatric patients in whom hemostasis was achieved was higher in the TachoSil group than the Surgicel Original group at both 3 minutes and 5 minutes and that the time to hemostasis for the pediatric patients was shorter in the TachoSil group than the Surgicel Original group. The results were generally similar across the pediatric age groups (0 to 23 months, 2 to 11 years, and 12 to 16 years) and similar to the adult data (although data for the adolescent group were limited). The results indicate that TachoSil is efficacious for use as an adjunct to hemostasis in hepatic resection surgery in adult and pediatric patients.

Corza has received approval for the extension of indication to paediatric population (children from 1 month of age) on 24 March 2023. The current SmPC states that TachoSil is indicated in adults and children aged 1 month 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, also in adults for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery

Evidence for the efficacy of TachoSil in support of the paediatric indication has also been demonstrated by its frequent off-label use recorded in literature.(Module 2.5 Clinical Overview)

This is also supported by the pivotal study TC-2402-040-SP, that compared TachoSil with Surgicel Original as adjunct to primary surgical treatment in both adult and paediatric subjects.

In addition, a prospective, uncontrolled study (TC-019-IN) in paediatric subjects provides additional experience with the use of TachoSil in children.

Thus, TachoSil has demonstrated an acceptable safety profile and is clinically appropriate for use in this population.

Elderly

All studies except TC-019-IN were conducted in adults aged at least 18 years within the range of 18-87 years of age in the controlled trials and with a mean age of 58.1 years (26.3% were aged 66 to < 75 years and 6.4% were aged 75 or over).

Pregnant or Breast Feeding Women

One non serious report of exposure to TachoSil during pregnancy was reported in clinical trials. The patient underwent elective termination of pregnancy (she was 10 weeks pregnant) due to her poor health status and high risk for her and her child.

Genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies have not been performed with TachoSil, since they are not considered to provide meaningful information for a risk-benefit evaluation.

No special or unknown risk is expected in a child under the circumstances of breastfeeding as it is not considered possible that any of the ingredients of TachoSil enter the milk. According to the current SmPC TachoSil should be administered to pregnant and lactating women only if clearly needed.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program, as not relevant for this type of product for local application
Population with relevant different ethnic origin	Not included in the clinical development program. The majority of patients included in the clinical trials were Caucasian except for TC-026-JP which included Japanese patients. The influence of ethnic origin has not been studied further concerning local treatment with TachoSil. No pharmacokinetic differences between the ethnic groups are expected.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program. Not relevant for this type of product.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Cumulative data since the International Birth Date (IBD) of 08 June 2004 till 08 June 2023 show that the total global exposure to TachoSil is approximately 11.63 million patient-years (as per PBRER with DLP 8 June 2023, under PSUSA/00010297/202306 submitted to EMA), assuming an average use of one patch per procedure and per patient.

Post-authorization (non-clinical trial) Exposure
Worldwide exposure cumulatively since launch till 08 June 2023 is approximately 11.63 million patient-years.

SV.1.1 Method used to calculate exposure

For TachoSil, the methodology used to calculate the exposure assumes an average use of one patch per procedure and per patient based on the current RSI.

SV.1.2 Exposure

Based on the above methodology, the patient exposure is [redacted] patients of treatment during the reporting period and 11.63 million patients of treatment cumulatively.

The patient exposure for TachoSil is presented in Table SV.1: and Table SV.2:.

Table SV.1:	**Patient exposure for TachoSil from marketing experience by region (patient-years)**		
Region	**Patients in Reporting period[a]**	**Cumulative patients since January 2007[b]**	**Cumulative patients since launch[c]**
European Union	[redacted]	7,140,534	N/A
Asia	[redacted]	335,215	N/A
[redacted]	[redacted]	[redacted]	[redacted]
*Rest of World (ROW)	[redacted]	2,383,423	N/A
[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	**11,269,363**	**11,633,169**

*For [redacted] sales data has been taken from the partner.
(a) Shipment data covers the period from 09 June 2020 to 08 June 2023.
(b) Shipment data covers the period from January 2007 to 08 June 2023.
(c) Shipment data covers the period from June 2004 to 08 June 2023. Cumulative historical data was not broken down by region. N/A- Not available.

Table SV.2	**Patient exposure for TachoSil from marketing experience dosage form (patient-years)**	
Region	**Patients in reporting period [a]**	**Cumulative patients since launch[b]**
Small	[redacted]	2,488,958
Medium[c]	[redacted]	3,350,532
Large	[redacted]	5,733,391
Not specified	0	20,288
Total	[redacted]	**11,633,169**

(a) Shipment data covers the period from 09 June 2020 to 08 June 2023.
(b) Shipment data covers the period from June 2004 to 08 June 2023.
(c) Medium size includes pre-rolled presentations.

Post-approval Use in Special Populations

Since the post-marketing exposure is based on sales/shipment data, it is not currently possible to present the exposure by gender, age, dose, dosage form or other factors. In addition, the Company has not conducted any non interventional studies (including registries) investigating post-approval use in special populations.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

TachoSil is not structurally or pharmacologically related to any drug known to cause abuse or dependence. The product PK and PD characteristics do not suggest any potential effect on CNS that may produce drug dependence. During the clinical development program there have been no AEs that would be indicative of abuse or a dependence potential and no behaviour or withdrawal symptoms were observed after stopping treatment.

TachoSil is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Foreign body reactions

As a sterile product TachoSil is highly unlikely to be the source of infection.

The nonclinical safety program for TachoSil included single- and repeat-dose studies and local tolerance studies with TachoSil or with its predecessor collagen patches Tachotop, TachoComb and TachoComb-H. The patches were tested either individually in the studies or in different combinations within 1 study. The results of the toxicity studies with TachoSil and its predecessors were comparable, reflecting the essential similarity in composition. Therefore, safety aspects for TachoSil are derived from the results obtained from preclinical studies with the related collagen patches. A subject weighing 70 kg treated with 1 TachoSil patch corresponds to a single dose of approximately 10 mg/kg. Considering that the clinical dose of TachoSil varies widely depending on the surgical situation, safety margins were determined to be at least 14 to 100 in rat studies and 7 to 50 in dog studies. In animal studies, TachoSil progressively degrades with only a few remnants left after approximately 13 weeks. Complete degradation of TachoSil was seen in some animals 12 months after administration to a liver wound, whereas small remnants were still observed in others. No evidence of local intolerability has been observed in animal studies.

In summary, the results of all preclinical studies confirmed an acceptable local tolerance profile for TachoSil and its predecessors TachoComb and TachoComb-H. Local reactions to the implants reflect the ongoing repair process and are considered to be a nontoxic response

Based on the results of the animal study, SmPC section 5.2 Pharmacokinetic properties mentions:

“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.”

During clinical trials, there were no reports of foreign body reactions.

As there were no events of foreign body reaction reported from clinical trials, and there were only three ICSRs reorted by previous MAH (Takeda), according to the last PBRER DLP 08 Jun 2021 this event is not considered to be an important identified or potential risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Pharmacological Class Effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/hemostatics. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen if the

preparation is applied repeatedly or administered to patients known to be hypersensitive to constituents of the product.

Antibodies against components of fibrin sealant/hemostatic products may occur rarely. In a clinical trial with TachoSil in hepatic surgery, in which patients were investigated for the development of antibodies, about 26% of the 96 patients tested and treated with human fibrinogen/human thrombin sponge (patch) developed antibodies to equine collagen. The equine collagen antibodies that developed in some patients after human fibrinogen/human thrombin sponge (patch) use were not reactive with human collagen One patient developed antibodies to human fibrinogen. There were no adverse events attributable to the development of human fibrinogen or equine collagen antibodies.

Thromboembolic complications may occur if the preparation is applied intravascularly.

When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential

Important Identified Risk: Thrombotic and embolic events (Using SMQ-Broad searches: Embolic and thrombotic events, arterial and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous; SMQ-narrow searches: Embolic and thrombotic events, arterial, Embolic and thrombotic events, venous and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	
Potential mechanisms	The mechanism of action of TachoSil follows the principles of physiological fibrin clot formation. Upon contact with a bleeding or leaking wound surface, or triggered by the presence of physiological saline, the coating of the collagen-sponge dissolves, and the subsequent thrombin-fibrinogen reaction initiates the last step of the coagulation cascade: Fibrinogen is converted by the action of thrombin into fibrin monomers which spontaneously polymerise to a fibrin clot. Thrombin may also activate endogenous factor XIII, which covalently crosslink's the fibrin to create a firm and stable network. A total of 299 large size TachoSil sponges were applied to 119 patients in the 2 liver resection trials, TC-014-IN and TC-016-IN, giving an average of 2.5 sponges per patient. In the lung trial, TC-013-IN, an average of 1.5 large size sponges was applied per patient. The amount of fibrinogen on one large size TachoSil sponge is 5.5 mg/cm^2 × (9.5 × 4.8) cm^2 equal to 250.8 mg. Thus, the amount of fibrinogen on 2.5 large size TachoSil sponge is 627 mg, which if instantly distributed into the total circulation of 3 litres of blood plasma (equivalent to 5.5 litres of whole blood) gives an increase in the plasma concentration of 209 µg/ml. The normal circulating fibrinogen concentration is approximately 3,000 µg/ml. The exogenous addition of fibrinogen by the application of 2.5 TachoSil sponges will thus theoretically increase the circulating fibrinogen concentration by 7%. The actual increase will only be a fraction of this, as the locally applied exogenous fibrinogen is immediately immobilised at the wound site by reaction with thrombin dissolved from TachoSil. However, a slightly increased plasma fibrinogen concentration is not in itself expected to increase the potential but rather the capacity of blood clotting, as conversion to fibrin depends on (local) activation of the clotting cascade. Thus, it is unlikely that a slightly increased circulating fibrinogen concentration would activate the clotting mechanism and induce thromboembolic complications. It seems physiologically irrelevant to compare the applied amount of thrombin with the free circulating thrombin, which occurs only temporarily as a derivative of prothrombin. It is expected that following the dissolution from the TachoSil sponge, the locally applied thrombin immediately reacts with fibrinogen and is thereby inactivated in-situ, with no or very little systemic presence.
Evidence source(s) and strength of evidence	Company and previous MAH (Takeda) safety database; RSI; Published Literature. <u>Clinical trials:</u> All Study Pool: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM, TC-023-IM, TC-2402-038-SP, TC-2402-040-SP. Paediatric Pool: TC-019-IN, paediatric subjects from TC-2402-040-SP. PASS Study: TC-018-IN. <u>Post-marketing:</u> Spontaneous including regulatory authorities (worldwide) and literature and non-interventional post-marketing studies.

Characterisation of the risk	**Frequency (clinical manifestations):** **Clinical trial data: IBD through 08 June 2020[a]:** A cumulative search of the Global Safety Database (GSDB) of previous MAH (Takeda), retrieved 45 cases (43 serious and 2 non-serious) containing 52 events (48 serious and 4 non-serious) with TachoSil as suspect drug from the previous MAH (Takeda)-sponsored trial. The reported PTs included arteriovenous graft thrombosis (n=7), acute myocardial infarction, cerebral ischemia, cerebrovascular accident, myocardial infarction, and vascular graft occlusion (n=4 each), cerebral infarction (n=3), pulmonary embolism, hepatic artery thrombosis, thrombosis, and vascular graft thrombosis (n=2 each), and 1 event each of arteriovenous fistula occlusion, disseminated intravascular coagulation, haemorrhagic cerebral infarction, hemiparesis, ischaemic stroke, lacunar infarction, peripheral arterial occlusive disease, portal vein thrombosis, pulmonary infarction, pulmonary thrombosis, quadriparesis, graft thrombosis, venous thrombosis limb and venous thrombosis. Seriousness/outcome: The outcome of the 52 events was reported as recovered (n=30), recovered with sequelae (n=9), fatal (n=5), not recovered (n=4) and recovering (n=4). A cumulative search of the GSDB of previous MAH (Takeda) also retrieved 1 serious case with 1 serious adverse event (PT: pulmonary embolism) from an investigator sponsored trial. Seriousness/outcome: The outcome of the serious event reported from the investigator-sponsored trial was reported as recovered. **Clinical trial data from 09 June 2020 to 08 June 2023[b]:** Not applicable as no clinical trials were conducted in the reporting period. **Post-marketing data: IBD through 08 June 2020:** A cumulative search of the GSDB of previous MAH (Takeda), retrieved 76 reports containing 83 events (77 serious and 6 non-serious) from post-marketing sources. The reported PTs included pulmonary embolism (n=26), deep vein thrombosis (n=11), thrombosis (n=4), embolism, portal vein thrombosis and cerebrovascular accident (n=3 each), post procedural pulmonary embolism, peripheral artery thrombosis, disseminated intravascular coagulation, subclavian vein thrombosis, myocardial infarction, pulmonary artery thrombosis and venous thrombosis (n=2 each) and 1 event each of cerebral artery thrombosis, cerebral infarction, coronary artery thrombosis, diplegia, hemiparesis, hepatic artery thrombosis, hepatic vein thrombosis, jugular vein thrombosis, mesenteric artery thrombosis, mesenteric vein thrombosis, paraplegia, pelvic venous thrombosis, renal artery thrombosis, retinal vein thrombosis, shunt occlusion, vena cava thrombosis**,** superior vena cava occlusion, superior vena cava syndrome, and venous occlusion. Seriousness/outcome: The outcome of the 83 events was reported as fatal (n=10), recovered (n=51), recovered with sequelae (n=8), recovering (n=1), unknown (n=9), and not reported (n=4). **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** Three cases containing 9 events (7 serious and 2 non-serious) was retrieved from the safety database from post-marketing sources. The reported PTs included one event each of cerebrovascular accident, cardiac failure congestive, cardio-respiratory arrest, vascular pseudoaneurysm, renal vein thrombosis, jugular vein thrombosis, subclavian vein thrombosis, therapeutic product effect incomplete (reported as complete haemostasis was difficult), and oedema peripheral. Seriousness/outcome: The outcome of the 9 events was reported as recovered (n=1), recovering (n=2), not reported (n=3), and unknown (n=3).

	Background incidence / prevalence: Among patients undergoing surgery for several cancers, identified in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2007-2009, the incidence of venous thromboembolism (VTE) within 1 month following surgery ranged from 0.28-7.28% (De Martino et al., 2012). The expected incidence of thromboembolic events in the PASS study population was 10-15% (Eriksen et al., 2005). This was based on a review of the available literature before finalisation of the study protocol. However, the review did not take into account that 8-9 out of 10 thromboembolic events are clinically silent and only detected if using a systematic approach, such as typically used in clinical trials focusing on prevention (Geerts et al., 2004, Mismetti et al., 2001, Badner et al, 1998). No such systematic approach was used in this non-interventional study, which explains the lower reported incidence of thromboembolic events. An expected background incidence for developing a thromboembolic event in the target population is therefore estimated to 1.0-3.0%. The protocol defined a thromboembolic event as "any coagulation-based occlusion in a vessel or in the heart whether identified by symptomatic clinical signs and verified by para clinical examinations such as ultrasound scan, Magnetic Resonance scanning, Computerised Tomography scanning or scintigraphy or only identified by these para clinical examinations." Thromboembolic events do occur quite frequently in patients who are bedridden after surgery. Prophylactic treatment with low molecular weight heparin is effective and very common; in the PASS study reflected by the most frequently used concomitant medications being heparins, used during or after surgery in 79% of all patients. **Severity and nature of risk:** In clinical trials, the severity of thrombotic and embolic events ranged from mild to severe in intensity. Therefore, Thrombotic, and embolic events could lead to hospitalisation and can potentially be fatal. See Seriousness/outcomes.
Risk factors and risk groups	Upon assessment of several patient-level variables in the ACS-NSQIP database, multivariate predictors of VTE among patients undergoing surgery for cancer included age (60-79 years), recent steroid use, body mass index ≥35 kg/m^2, and post-operative complications, including wound infection, reintubation, cardiac arrest, and sepsis (De Martino et al., 2012). Among a veteran's affairs NSQIP population, factors found to be strong positive predictors of symptomatic VTE included urinary tract infection, acute renal insufficiency, post-operative transfusion, perioperative myocardial infarction, and pneumonia (Gangireddy et al., 2007). Known risk factors for thromboembolic events recorded in the PASS study are: cardiovascular risk factors (atherosclerosis, angina pectoris, chronic atrial fibrillation, congestive heart failure, own or family history of thromboembolic event, hypercholesterolemia, hypertension, inherited hypercoagulable states, ischaemic heart failure, left ventricular hypertrophy, smoking, varicose veins), chronic obstructive pulmonary disease, cancer, diabetes mellitus, hormone therapy, hypothyroidism, pregnancy, sepsis, and abnormal electrocardiogram. The majority of patients (2,813, 90.8%) had a risk factor for thromboembolic events prior to surgery; the most common of these were cardiovascular risk factors (2,135 patients, 68.9%) which included own or family history of thromboembolic event (64 patients, 2.1%) and/or at least one other cardiovascular risk factor (2,122 patients, 68.5%); and cancer (1,597 patients, 51.5%).
Preventability	TachoSil is not intended for use on any endovascular surface since the outcome may be local thrombosis and/or embolism. The likelihood of reagents contained in the TachoSil accidentally being brought into systemic circulation is extremely low if guidance in the label relating to intravascular use is adhered to.

Reversibility	Treatment with anticoagulants and surgical procedures such as thrombectomy, embolectomy, or surgical removal of the embolised product.
Impact on the risk-benefit balance of the product:	Effect on individual patient will vary depending on the severity and location of the thromboembolism.
Public health impact	Based on data from the integrated dataset the expected number of patients affected by a thromboembolic event is 1.92% (95%-Confidence interval [CI]: 0.92% to 3.50%). This is however not expected to be due to treatment with TachoSil, but due to the surgical procedure and the underlying disease. Thromboembolic events are expected only if TachoSil is applied intravascularly.
Important Identified Risk: Immunological events including hypersensitivity (Using SMQ-Broadsearch: Hypersensitivity; SMQ-Narrow search: Hypersensitivity)	

Potential mechanisms	TachoSil is a sponge consisting of equine collagen coated with a layer of human fibrinogen and human thrombin. Thus, equine collagen is a species foreign constituent in TachoSil in relation to humans. In general, an organism will mount immune responses only against foreign antigens. In patients treated with TachoSil, the possibility that equine collagen might be recognised as a foreign antigen by the immune system exists. Preclinical investigations concerning the immunogenic potential of the components of TachoSil revealed that human fibrinogen induced positive reactions in guinea pigs, indicated by the formation of antibodies. The equine collagen component of TachoSil is not expected to induce an immunological response under clinical conditions as there is a high similarity between human and equine collagen type 1. However, during testing of antibodies against the components of TachoSil in TC-2402-040-SP, Liver surgery, 25 TachoSil treated adult subjects out of 96 tested developed equine directed antibodies. Additionally, 1 subject developed antibody to human fibrinogen, identified in the follow-up period at 1 month, 3 months or both. These subjects were followed up for 24 months and did not report any adverse events suggestive of immunogenic reactions related to the presence of these antibodies and no reports suggesting any clinical impact on the haemostatic effect of TachoSil have been discovered. Moreover, TachoSil is not intended for regular repeated administration to humans and chances of repeated application are usually very low.
Evidence source(s) and strength of evidence	Company and previous MAH (Takeda) safety database; RSI; Published Literature. Clinical trials: All Study Pool: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM, TC-023-IM, TC-2402-038-SP, TC-2402-040-SP. Paediatric Pool: TC-019-IN, paediatric subjects from TC-2402-040-SP. PASS Study: TC-018-IN. Post-marketing: Spontaneous including regulatory authorities (worldwide) and literature, and non-interventional post-marketing studies.

Characterization of the risk:	**Frequency (clinical manifestations):** **Clinical data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 9 cases (8 serious and 1 non-serious) containing 10 events (9 serious and 1 non-serious) with TachoSil as suspect drug from the previous MAH (Takeda)-sponsored trial. The reported PTs included respiratory failure (n=5) and 1 event each of the following events circulatory collapse, laryngeal oedema, pruritus, respiratory distress, and shock. Seriousness/outcome: The outcome of the 10 events were reported as fatal (n=2), not recovered (n=1), recovered (n=5) and recovered with sequelae (n=2). A cumulative search of the GSDB also retrieved 4 cases (1 serious and 3 non-serious) with 4 events (1 serious and 3 non-serious). The PTs reported were scrotal oedema (n=3) and visceral oedema (n=1) from an investigator-sponsored trial. Seriousness/outcome: The outcome of all the 4 events (1 serious and 3 non-serious) reported from the investigator-sponsored trial was reported as recovered. **Clinical trial data from 09 June 2020 to 08 June 2023[b]:** Not applicable as no clinical trials were conducted in the reporting period. **Post-marketing data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 32 reports, containing 33 events (18 serious and 15 non-serious). The reported PTs included anaphylactic reaction (n=2), anaphylactic shock (n=4), angioedema (n=1), application site hypersensitivity (n=2), bronchospasm (n=1), circulatory collapse (n=4), dermatitis (n=1), drug hypersensitivity (n=2), hypersensitivity (n=2), laryngeal oedema (n=2), rash (n=3), rash pruritic (n=1), shock (n=3), swelling face (n=1), toxic skin eruption (n=1), and urticaria (n=3). Cumulatively, 32 reports including 33 events were reported (18 serious and 15 non-serious). The outcome of the 61 events were reported as fatal (n=4), recovered (n=19), recovering (n=5), unknown/not reported (n=4) and not recovered (n=1). **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** A cumulative search of the GSDB (from IBD to 08 Jun 2023), retrieved 49 reports and 49 events using the search for the above mentioned PTs. The current MAH, Corza, has included an additional PT in this category of interstitial lung disease: one serious case of a 75-year-old man containing 8 events (7 serious and 1 non-serious) was retrieved from the safety database from post-marketing source. The reported PTs included one event each of interstitial lung disease, haemorrhage, pulmonary air leakage, subcutaneous emphysema, C-reactive protein increased, infectious pleural effusion, pleural effusion, and pyrexia. The patient died due to event of acute aggravation of interstitial pneumonia. The outcome of other events was not reported. The death occurred 128 days after the application of TachoSil. It is biologically implausible that TachoSil would have caused acute aggravation of interstitial pneumonia. Seriousness/outcome: The outcome of the 49 events was reported as fatal (n=2), recovered (n=34),recovering (n=4), unknown (n=9). **Background incidence / prevalence:** General Population: The lifetime prevalence of anaphylaxis is estimated at 0.05-2.0% or approximately 50-2000 episodes per 100,000 persons (Lieberman et al, 2006). Based upon data from a systematic review, the incidence rates for all-cause anaphylaxis ranged from 1.5 to 7.9 per 100,000 person-years in Europe (Panesar et al, 2013). The average annual incidence of anaphylaxis in the general population among residents of Olmsted County, Minnesota in the US, between 1983 and 1987, was 21 per 100,000 person-years (Yocum et al, 1999).

	Severity and nature of risk: In clinical trials, the severity of Immunological events ranged from mild to severe in intensity. Therefore, Immunological events including hypersensitivity could lead to hospitalisation and can potentially be fatal. See Seriousness/outcomes.
Risk factors and risk groups:	Patients with a history of immune system disorders or multiple allergies may be at greater risk of a hypersensitivity reaction to TachoSil. Comorbid disease, including atopic eczema/dermatitis and asthma may be associated with increased risk of anaphylaxis (Panesar et al, 2013).
Preventability	Patients with a history of multiple allergies or immune or autoimmune disorders may be at greater risk of a hypersensitivity reaction to TachoSil.
Reversibility	Hypersensitivity reactions are treatable and the standard of care may include intramuscular adrenaline, corticosteroids, antihistamine, respiratory and/or vassopresor support if needed.
Impact on the risk-benefit balance	Impact on individual patient will vary depending on the severity of the hypersensitivity reaction. The development of antibodies against the component of TachoSil appeared to have minimal to no clinical impact.
Public health impact	The low number of reported events of hypersensitivity reactions indicate minimal public health impact.
Important Identified Risk: Gastrointestinal obstruction **(Using SMQ-narrow search: Gastrointestinal obstruction;** **MedDRA term PTs: Gastrointestinal obstruction, Abdominal adhesions, Pelvic adhesions, Peritoneal adhesions, Postoperative adhesion and Postoperative adhesion**	

Potential mechanisms	TachoSil can stick to the surrounding/adjacent surfaces that may be covered with blood if the surgical site is inadequately prepared and/or not cleansed of residual blood, or if TachoSil is applied inappropriately.
Evidence source(s) and strength of evidence	Company and previous MAH (Takeda) safety database; RSI; Published Literature. The main reasons for considering GI obstruction as an important identified risk is from Post-marketing case reports.
Characterization of the risk:	**Frequency (clinical manifestations):** **Clinical data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 6 serious cases reporting 6 serious events with TachoSil as suspect drug from the previous MAH (Takeda)-sponsored trial. The reported PTs included impaired gastric emptying (n=2), small intestinal obstruction (n=2), ileus (n=1) and post-operative adhesion (n=1). Seriousness/outcome: The outcome of the 6 reported events was reported as recovered. A cumulative search of the GSDB also retrieved 1 serious case with 1 serious event (PT: impaired gastric emptying) from an investigator-sponsored trial. Seriousness/outcome: The outcome of 1 serious event reported from the investigator-sponsored trial was reported as recovered. **Clinical trial data from 09 June 2020 to 08 June 2023[b]:** Not applicable as no clinical trials were conducted in the reporting period. **Post-marketing data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 14 cases (11 serious and 3 non-serious), containing 14 events (11 serious and 3 non-serious). The reported PTs included intestinal obstruction (n=6), adhesion (n=3), abdominal adhesions and ileus (n=2 each) and sub ileus (n=1). The proportion of GI adhesion/obstruction cases received relative to the total number of cases received for TachoSil was 1.86% (25/1,337). Cumulatively, 27 cases were reported for off-label use in GI anastomosis. Of these. 2 cases were serious. The associated PTs of adverse events included fistula (n=1) and peritoneal haemorrhage (n=1). The frequency of the risk could not be calculated and is unknown. Seriousness/outcome: The events outcome was reported as recovered (n=7), not recovered (n=1), not reported (n=2) and unknown (n=4). The outcome of the adverse events associated with the 2 serious cases of GI anastomosis was unknown/not reported. **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** No new cases retrieved from the safety database. **Background incidence / prevalence:** 50%-93% of patients that undergo abdominopelvic surgery will develop adhesions (Attard et al, 2007, Hellebrekers et al, 2011, Munireddy et al., 2010, Ouaissi et al, 2012). Bowel obstruction is a common complication of surgery secondary to the formation of post-surgical adhesions. 60% to 70% of all small bowel obstruction (SBO) in industrialised countries are a result of abdominal adhesions (Ellis et al., 1998, Parker et al., 2001). In a systematic review the incidence of SBO following surgery was assessed (ten Broek et al., 2013)- 61 studies including 107,949 patients that underwent abdominal surgery reported an incidence of post-operative SBO, by any cause, of 9%; in 87 studies including 110,076 patients, the incidence of adhesive SBO was found to be 2.4%. In another systematic review of 446,331 abdominal operations, (Barmparas et al., 2010) an overall incidence of adhesive SBO of 4.6% was reported. **Severity and nature of risk:** GI obstruction could lead to hospitalisation and requiring surgical intervention and can potentially be fatal. See Seriousness/outcomes.

Risk factors and risk groups	TachoSil is used in both abdominal and non-abdominal surgical indications. The risk of GI obstruction concerns the group who undergo abdominal surgeries only. The risk of adhesion and subsequent obstruction increases if the surgical site and adjacent tissues are inadequately prepared and/or cleansed of residual blood. There are a number of potential risk factors for development of adhesions in patients that undergo abdominal surgery including longer operative time and prior abdominal surgeries (Sastry et al., 2015).
Preventability	To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before application of TachoSil. There is some evidence that correct application of TachoSil may prevent post-operative adhesions. In a swine study (Pérez et al., 2011) evaluating the preventive effect of TachoSil on adhesion formation in conventional (n=20) and laparoscopic (n=20) hysterotomy and simulated adhesiolysis 5-months following initial operation, (Pérez et al., 2011) observed significant reduction ($p<0.05$) in rate, severity, tenacity and extent of adhesion formation in the right and left uterine horn in the TachoSil group compared to the control group.
Reversibility	Surgical adhesiolysis may be required to treat GI obstructions due to adhesions.
Impact on the risk-benefit balance of the product	GI obstruction could potentially lead to re-surgery and re- or prolonged hospitalisation. For patients with a history of prior bowel obstruction, the likelihood of recurrent obstruction increases with an increasing number of episodes (Barkan et al., 1995, Miller et al, 2000). Patients with recurrent obstructions often have a limited or liquid diet requirement, experience pain in multiple areas of their bodies, and have GI symptoms that impact their quality of life including bloating, nausea, vomiting, diarrhoea or constipation and the inability to perform everyday activities (Rice et al, 2014).
Public health impact	The public health impact of tissue adhesions leading to GI obstruction is unknown.

Abbreviations: ACS-NSQIP = American College of Surgeons National Surgical Quality Improvement Program; EU = European Union; GI = Gastrointestinal; GSDB = Global Safety Database; IBD = International Birth Date; IU = International Unit; MAH = Marketing Authorisation Holder; PASS = Post-authorisation Safety Studies; PBRER = Periodic Benefit-Risk Evaluation Report; PT = Preferred term; RSI = Reference Safety Information; SBO = Small bowel obstruction; US = United States; VTE = Venous thromboembolism.

a Source: Previous EU PBRER with reporting period 09 June 2019 to 08 June 2020, prepared by Takeda (former MAH).

b Source: Cases retrieved from the search of safety database by the Company for the reporting period 09 June 2020 to 08 June 2023

Important Potential Risk: Transmission of infectious agents (Using MedDRA terms <u>High-LevelTerms:</u> Hepatitis virus infections, Infectious transmissions, Parvoviral infections, Prion-associated disorders, Retroviral infections and Virus identification and serology	
Potential mechanisms	Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia). It is strongly recommended that every time TachoSil is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.
Evidence source(s) and strength of evidence	Company and previous MAH (Takeda) safety database; RSI; Published Literature. <u>Clinical trials:</u> All Study Pool: TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM, TC-023-IM, TC-2402-038-SP, TC-2402-040-SP. Paediatric Pool: TC-019-IN, paediatric subjects from TC-2402-040-SP. PASS Study: TC-018-IN. <u>Post-marketing:</u> Spontaneous including regulatory authorities (worldwide) and literature and non-interventional post-marketing studies.

Characterization of the risk	**Clinical data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 2 cases (1 serious and 1 non-serious) reporting 2 events (1 serious and 1 non-serious) with TachoSil as suspect drug from the previous MAH (Takeda)-sponsored trial. The reported PTs included hepatitis B antibody positive (n=1) and hepatitis B antigen positive (n=1). Seriousness/outcome: The outcome of the 2 reported events was reported as recovering (n=1) and not reported (n=1). **Clinical trial data from 09 June 2020 to 08 June 2023[b]:** Not applicable as no clinical trials were conducted in the reporting period. **Post-marketing data: IBD through 08 June 2020[a]:** A cumulative search of the GSDB, retrieved 13 cases (9 serious and 4 non-serious) containing 16 events (11 serious and 5 non-serious) with TachoSil as suspect drug. The reported PTs included hepatitis C (n=7), hepatitis C antibody positive (n=3), hepatitis C virus test positive, hepatitis E, human immunodeficiency virus (HIV) test positive, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test positive, suspected transmission of an infectious agent via product and transmission of an infectious agent via product (n=1 each). Seriousness/outcome: The outcome of the 16 events was reported as recovered (n=1), recovering (n=1), not recovered (n=2), not reported (n=2) and unknown (n=10). The Company has investigated the lots of human fibrinogen and human thrombin used in the production of the TachoSil sponges used in these patients. Different lots of fibrinogen and thrombin were used in each patient and each of the lots of fibrinogen and thrombin had been produced from hepatitis C virus-polymerase chain reaction (HCV-PCR) non-reactive plasma pools. The production includes steps to inactivate/eliminate potentially infectious viruses with a high safety margin. These steps have been thoroughly validated. Each lot has been individually “batch-released” by the Paul-Ehrlich-Institute. Therefore, it was jointly concluded that there was no temporal or lot-related cluster of case reports, and a causal relationship between TachoSil and the 3 cases of hepatitis C and the 1 case of hepatitis E was considered unlikely. The Company considers that the controls in place during production ensure that the viral safety of TachoSil is acceptable. **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** No new cases retrieved from the safety database. **Background incidence/ prevalence:** General Population: Based upon data from systematic reviews, the 2005 global prevalence of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) was estimated at 3.7% and 2.8%, respectively (Ott et al., 2012, Mohd Hanafiah et al., 2013). More recent epidemiology (2015) estimates HBsAg seroprevalence was 3·61% and viremic hepatitis C as 1.0% of the world population (Schweitzer A et al, 2015, Jafri SM et al, 2018). Based upon data from the World Health Organization (WHO) Health for All Database, the average annual incidence rates for acute hepatitis C across countries in Europe ranged from 0.00 to 39.21 cases per 100,000 residents; and applying a population size weight yielded an average annual incidence rate of 6.19 per 100,000 for the WHO European region (excluding Monaco and Turkey) (Muhlberger et al., 2009). Based on data from the Joint United Nations Program on HIV/ Acquired immunodeficiency syndrome (AIDS) (United Nations Programme on HIV and AIDS [UNAIDS]) and WHO, the 2007 global prevalence of HIV-1 infection was 0.8% and the annual incidence was estimated at 2.7 million in 2007 (Kilmarx et al., 2009). Since 2010, new HIV infections have declined by 38%, from 2.1 million [1.6 million– 2.8 million] to 1.3 million [1 million–1.7 million] in 2022.(NAIDS, 2023) Transmission rates for transfusion-transmitted viral infections have been reported in the

	literature using data collected for blood donations. Estimates of residual risk of transfusion-transmitted viral infection reported from studies conducted in the US were as follows: HBV (0.28-0.36 per 100,000 donations), HCV (0.87 per million donations), and HIV (0.68 per million donations) (Zou et al., 2009, Zou et al., 2010). In a study conducted in France, estimates of residual risk of transfusion-transmitted viral infections during the period from 1998 to 2000 were as follows: HBV (2.13 per million donations), HCV (1.16 per million donations) and HIV (0.73 per million donations) (Pillonel et al., 2002). However, process improvements for plasma derived products are thought to have led to a reduction in pathogen transmission by purified blood products. In 1 study assessing the safety margin for pathogen transmission for fibrin sealants licensed in the US and for thrombin, the calculated residual risk of transmission was found to be less than 1 in 10^{15} per vial for HIV, HCV, HBV and hepatitis A virus for both fibrinogen and thrombin (Horowitz et al., 2008). The calculated risk for parvovirus transmission was 1 in 500,000 vials for fibrinogen and less than 1 in 10^{7} per vial for thrombin. **Severity and nature of risk:** See Seriousness/Outcomes.
Risk factors and risk groups:	Many of the patients undergoing major surgical procedures are likely to have many comorbid conditions. They are also likely to require transfusion of blood or blood products before or after the surgery and thus are more likely to have transmission of infectious agents from the transfusion.
Preventability	See Potential Mechanism.
Reversibility	Not applicable
Impact on the risk-benefit balance of the product	Globally, disability-adjusted life-years (DALYs; the sum of years of life lost and years lived with disability) lost due to HBV, HCV, and HIV in 2010 were estimated at 68, 8, and 1184 per 100,000 populations, and were increased during the 20-year period from 1990 to 2010 (Murray et al., 2012). In the WHO European region, nearly 1.2 million DALYs were lost due to HCV in 2002, corresponding to an overall rate of 134.54 DALYs per 100,000 residents (Muhlberger et al., 2009). All 4 reports of hepatitis are considered unlikely related to TachoSil. The standard validated preventive measures during manufacturing of TachoSil to prevent infections are thorough and rigorous. To date, there is no evidence of an impact on individual patient.
Public health impact	See Background Incidence/prevalence section above. There are no confirmed cases of transmission of infectious agents associated with the use of TachoSil. No public health impact is anticipated.

Details of Missing information

Missing Information: Lack of experience in gastrointestinal anastomosis surgery (Using MedDRA term PTs: Off label use, Biliary anastomosis, Biliary anastomosis complication, Intestinal anastomosis, Intestinal anastomosis complication, Large intestine anastomosis, Oesophageal anastomosis, Small intestinal anastomosis, Post procedural bile leak)	
Evidence source(s) and strength of evidence:	**Post-marketing data: IBD through 08 June 2020[a]:** Cumulatively, 1 serious case with 1 serious event (PT: off-label use) of "Lack of Experience in Gastrointestinal Anastomosis Surgery" was retrieved from post-marketing sources. The event outcome was reported as unknown. The reporter causality was reported as related. **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** Zanatta, et al (2022) described the adjunctive use of TachoSil in gastrointestinal anastomosis surgery. TachoSil was applied to "straighten the gallbladder suture, to prevent the development of biliary fistulas" after subtotal cholecystectomy for Mirizzi syndrome. The case was databased under Reference number: 2022-IT-002180.
Missing Information: Lack of experience in pregnant or lactating women (Using MedDRA term PTs: Exposure during pregnancy, Foetal exposure during pregnancy, Maternal exposure during pregnancy, Paternal exposure during pregnancy; SMQ-Narrow search: Neonatal exposures via breast milk)	
Evidence source(s) and strength of evidence	**Post-marketing data: IBD through 08 June 2020[a]:** During this period, there have been no new case reports of exposure to TachoSil during pregnancy or lactation. **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** A search of the safety database retrieved 4 serious cases containing 5 events (3 serious and 2 non-serious) of exposure to TachoSil during pregnancy from post-marketing sources. The reported PTs included maternal exposure during pregnancy (n=1), exposure during pregnancy (n=2), premature baby (n=1), and foetal exposure during pregnancy (n=1). In 1st case, on 35 weeks and 6 days of gestation, a baby girl was born through vaginal delivery. The baby was hospitalised in the neonatal intensive care unit for premature delivery and low birth weight. The clinical course was favourable, and the baby was discharged from the hospital at 17 days-old without any remarkable abnormality. In 2nd case, the patient delivered healthy baby but had significant post-partum haemorrhages despite receiving fibrinogen concentrate. In 3rd case, the patient delivered a premature baby at 33 to 36 weeks of gestation. In last case, the delivery occurred on an unknown date with unknown outcome. All events (except for maternal exposure during pregnancy) were related to TachoSil.
Missing Information: Repeated use of TachoSil (Using MedDRA term: SOC Immune system disorders and PT: Surgical procedure repeated)	
Evidence source(s) and strength of evidence	**Post-marketing data: IBD through 08 June 2020[a]:** Cumulatively, 11 cases were reported with 11 events (7 serious and 4 non-serious events) from post-marketing sources. The PTs of 11 events were anaphylactic reaction (n=2), anaphylactic shock (n=4), drug hypersensitivity (n=2), graft versus host disease (n=1) and hypersensitivity(n=2). **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** No new cases retrieved from the safety database.
Missing Information: Use in paediatric population[c]	

Details of Missing information

Evidence source(s) and strength of evidence	**Post-marketing data: IBD through 08 June 2020[a]:** A search of the safety database retrieved 30 cases (1 serious and 29 non-serious cases) of TachoSil use in child/paediatric patient (PT: off-label use) from post-marketing sources. The events outcome was reported as not reported (n=2), recovered/resolved (n=1), and unknown (n=27). **Post-marketing data from 09 June 2020 to 08 June 2023[b]:** A search of the safety database retrieved 3 non-serious cases with 3 non-serious events of TachoSil use in paediatric patient from post-marketing sources. A case of 13-year-old boy with congenital lobar emphysema during the procedure of thoracotomy TachoSil patch was used for ensuring air-tight closure of the right upper bronchus (PT: off-label use). No complication was observed. No adverse events were reported. The other 2 cases (PT: off-label use) involved the use of TachoSil in a 14-year-old girl during a mastoidectomy procedure. No adverse events were reported. The outcome of all 3 events was unknown.

Abbreviations: EU = European Union; IBD = International Birth Date; MAH = Marketing Authorisation Holder; PBRER = Periodic Benefit-Risk Evaluation Report; PT = Preferred term; RMP = Risk Management Plan.

a Source: Previous EU PBRER with reporting period 09 June 2019 to 08 June 2020, prepared by Takeda (former MAH).

b Source: Cases retrieved from the search of safety database by the Company for the reporting period 09 June 2020 to 08 June 2023.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of 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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Routine pharmacovigilance activities will allow the monitoring and follow-up of any concern which may arise and facilitate the modification and/or planning of further actions than those detailed below. In any case, any eventual future recommendations from the PRAC, CHMP or Heads of Medicines Agencies (CMDh) as well as National Competent Authorities (NCAs) on the proposed activities will be considered and applied. Consequently, the Pharmacovigilance Plan of the aforementioned product will be updated accordingly.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are sufficient to address any safety concerns, with the supplementary areas of focus described below:

Other forms of routine pharmacovigilance activities for safety concerns

As this product is a biological product, particular attention will be paid to the identification of product names and batch numbers during the collection and processing of Individual Case Safety Reports (ICSRs) in the post-marketing setting. This includes:

- Ensuring that training provided to Corza staff on collection of safety data includes a requirement to request confirmation of the product name and batch number;
- Ensuring vendors involved in pharmacovigilance activities are instructed to collect product names and batch numbers from ICSR reporters, e.g. medical information vendors, pharmacovigilance vendors;
- Ensuring that distribution and/or licensing partners involved in product commercialisation are instructed to collect product names and batch numbers from ICSR reporters.

These requirements will be documented in applicable company procedures and inter-company contractual documents, such as Pharmacovigilance Agreements and Safety Data Exchange Agreements. The nature of ICSR reporting in the post-marketing setting is such that reporters often do not provide this information. Corza is establishing options that would facilitate easy recording of product name and batch information for individual patient doses, hopefully increasing the likelihood of this information being available upon Corza's request. As part of the sub-section Traceability of Section 4.4 – Special warnings and precautions of the SmPC, instructions are provided to healthcare professionals to record the name of the administered product in the patient file in order to improve the traceability of the medicinal product.

Corza will establish a signal detection process to review ICSRs collected in the post-marketing setting to detect any new safety concerns or any changes in understanding of existing safety concerns. This methodology will be supplemented by a review of data stratified by reported batch numbers to determine if the safety profile demonstrates a significant difference between batches.

III.2 Additional pharmacovigilance activities .

PASS-TachoSil Evaluation (PasTel) summary:

PASS-TachoSil Evaluation (PasTel) –observational study aiming to perform short and long-term safety evaluation of TachoSil in paediatric population.

Rationale and study objectives:

Corza proposed an extension of the indication to include paediatric population (children [redacted], which was approved by European Medicines Agency (EMA) on 24 March 2023. In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation safety study (PASS) will be performed: PASS-TachoSil Evaluation (PasTel). The study is conducted in order to [redacted].

The main purpose of the observational study is to collect long-term safety data on the use of fibrin sealant TachoSil during surgical procedures in paediatric population and to estimate the frequency of adverse reactions over a period of time, extending beyond TachoSil exposure, in a paediatric population of subjects who have been exposed to TachoSil. The study also aims to generate new data to confirm short-term safety of TachoSil in paediatric patients within proposed indication.

Primary endpoint:

Evaluation of [redacted] safety, including the risk of [redacted], of TachoSil up to [redacted] follow-up post-surgery period.

Secondary endpoints:

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Study design:

This is a prospective, multicentre, non-interventional, uncontrolled, observational, post-authorisation cohort study.

Study population:

The study population covers paediatric patients [redacted]

Data will be collected from the following age groups (age at the time of surgery):

- [redacted]
- [redacted]
- [redacted]

The following individuals may be eligible to participate:

- [redacted]
- [redacted]
- [redacted]

Patients are excluded from the study if:

- [redacted]
- [redacted]
- [redacted]

Milestones:

Start of data collection: [redacted]

End of data collection: [redacted]

Registration in the EU PASS register: [redacted]

Annual study progress report [redacted] Interim study report [redacted]

Final report of study results: [redacted]

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.3 Ongoing and Planned Additional Pharmacovigilance Studies

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
Prospective, observational, post-authorisation cohort study (PASS-TachoSil Evaluation (PasTel)) Planned	**Primary objective:** • Evaluation of [redacted] safety, including the risk [redacted] of TachoSil up to [redacted] follow-up post-surgery period **Secondary objectives:** - [redacted] • Determination of [redacted]	**Missing information on long-term outcomes of Tachosil use in:** • paediatric population	Registration in the EU PASS register Start of data collection Annual study progress report Interim study report End of data collection Final Report	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]

	[redacted]			

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

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.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern		**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks	Thrombotic and embolic events	Routine risk minimisation measures: *SmPC section 4.2, 4.3, 4.4 and section 4.8* *PL Section 2, Warning and precautions*	Routine pharmacovigilance activities
Important identified risks	Immunological events including hypersensitivity	*SmPC section 4.2, 4.3, 4.4 and section 4.8* *PL Section 2, Warning and precautions*	Routine pharmacovigilance activities
Important identified risks	Gastrointestinal obstruction	*SmPC section 4.2, 4.4. 4.8, 6.6* *PL Section 2, Warning and precautions*	Routine pharmacovigilance activities
Important potential risks	Transmission of infectious agents	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety concern		**Risk minimisation measures**	**Pharmacovigilance activities**
		SmPC section 4.4 and section 6.6 *PL Section 2, Warning and precautions*	
Missing information	Lack of experience in gastrointestinal anastomosis surgery	Routine risk minimisation measures: *SmPC section 4.4*	Routine pharmacovigilance activities
	Lack of experience in pregnant or lactating women	Routine risk minimisation measures: *SmPC section 4.6*	Routine pharmacovigilance activities
Missing information	Repeated use of TachoSil	Routine risk minimisation measures: *SmPC section 4.8* PL Sec. 4	Routine pharmacovigilance activities
Missing information	Use in paediatric population	Routine risk minimisation measures: *SmPC section 4.2,5.1* PL Sec. 2	Routine pharmacovigilance activities Additional pharmacovigilance activities: PASS-TachoSil Evaluation (PasTel).

Part VI: Summary of risk management plan for TachoSil (Human Fibrinogen, Human Thrombin)

This is a summary of the risk management plan (RMP) for TachoSil. The RMP details important risks of TachoSil, how these risks can be minimised, and how more information will be obtained about TachoSil risks and uncertainties (missing information).

TachoSil summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TachoSilstre should be used.

This summary of the RMP for TachoSil should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TachoSil RMP.

I. The medicine and what it is used for

TachoSil is indicated in adults and children aged 1 month 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.

TachoSil is indicated in adult sfor supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery.

Further information about the evaluation of TachoSil's benefits can be found in TachoSil's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/tachosil* link to the EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TachoSil, together with measures to minimise such risks and the proposed studies for learning more about TachoSil's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of TachoSil is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TachoSil, are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TachoSil. Potential risks are concerns for which an association with the use of this medicine is possible

based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected;

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

II.B Summary of important risks

Important identified risk Thrombotic and embolic events	
Evidence for linking the risk to the medicine	Treatment with Tachosil, may lead to the development of thrombotic and embolic events. Thromboembolic complications may occur if the preparation is applied intravascularly. Based on data from the integrated dataset the expected number of patients affected by a thromboembolic event is 1.92% (95%-CI: 0.92% to 3.50%). This is however not expected to be due to treatment with TachoSil, but due to the surgical procedure and the underlying disease. Thromboembolic events are expected only if TachoSil is applied intravascularly. There were 52 reported events of thrombotic and embolic events during clinical studies with TachoSil and 91 events from post-marketing sources.
Risk factors and risk groups	Known risk factors for thromboembolic events are: cardiovascular risk factors (atherosclerosis, angina pectoris, chronic atrial fibrillation, congestive heart failure, own or family history of thromboembolic event, hypercholesterolemia, hypertension, inherited hypercoagulable states, ischemic heart failure, left ventricular hypertrophy, smoking, varicose veins), chronic obstructive pulmonary disease, cancer, diabetes mellitus, hormone therapy, hypothyroidism, pregnancy, sepsis, and abnormal electrocardiogram, age (60-79 years), recent steroid use, body mass index≥35 kg/m2, and postoperative complications, including wound infection, reintubation, cardiac arrest, urinary tract infection, acute renal insufficiency, postoperative transfusion, perioperative myocardial infarction, and pneumonia.
Risk minimisation measures	Routine risk minimisation measures SmPC Sec. 4.2, 4.3, 4.4, 4.8 PL Sec. 2
Additional pharmacovigilance activities	Not applicable

Important identified risk Immunological events including hypersensitivity	
Evidence for linking the risk to the medicine	Treatment with TachoSil may lead to the development of hypersensitivity. There were 14 reported events of hypersensitivity during clinical studies with TachoSil and 82 events from post-marketing sources.
Risk factors and risk groups	Patients with a history of immune system disorders or multiple allergies may be at greater risk of a hypersensitivity reaction to TachoSil.

	Comorbid disease, including atopic eczema/dermatitis and asthma may be associated with increased risk of anaphylaxis [8].
Risk minimisation measures	Routine risk minimisation measures SmPC Sec. 4.2, 4.3, 4.4, 4.8 PL Sec. 2
Additional pharmacovigilance activities	Not applicable

Important identified risk Gastrointestinal obstruction	
Evidence for linking the risk to the medicine	TachoSil can stick to the surrounding/adjacent surfaces that may be covered with blood if the surgical site is inadequately prepared and/or not cleansed of residual blood, or if TachoSil is applied inappropriately. There were 7 reported events of gastrointestinal obstruction during clinical studies with TachoSil and 14 events from post-marketing sources.
Risk factors and risk groups	TachoSil is used in both abdominal and non-abdominal surgical indications. The risk of GI obstruction concerns the group who undergo abdominal surgeries only. The risk of adhesion and subsequent obstruction increases if the surgical site and adjacent tissues are inadequately prepared and/or cleansed of residual blood. There are a number of potential risk factors for development of adhesions in patients that undergo abdominal surgery including longer operative time and prior abdominal surgeries [18].
Risk minimisation measures	Routine risk minimisation measures SmPC Sec. 4.2, 4.4. 4.8, 6.6 PL Sec. 2
Additional pharmacovigilance activities	Not applicable

Important potential risk : Transmission of infectious agents	
Evidence for linking the risk to the medicine	When medicines, like Tachosil are prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. There were 2 reported events of transmission of infectious agents during clinical studies with TachoSil and 16 events from post-marketing sources, but there are no confirmed cases of transmission of infectious agents associated with the use of TachoSil.
Risk factors and risk groups	Many of the patients undergoing major surgical procedures are likely to have many comorbid conditions. They are also likely to require transfusion of blood or blood products before or after the surgery and thus are more likely to have transmission of infectious agents from the transfusion.

Risk minimisation measures	Routine risk minimisation measures SmPC Sec. 4.4, 6.6 PL Sec. 2
Additional pharmacovigilance activities	Not applicable

Missing information Lack of experience in gastrointestinal anastomosis surgery	
Evidence for linking the risk to the medicine	There is insufficient information on the use of TachoSil in gastrointestinal anastomoses surgery. Cumulatively, 2 cases were retrieved from post-marketing sources: one serious case with one serious event and one non-serious case with 1 non-serious event (PT: Off-label use) evidence of “Lack of Experience in Gastrointestinal Anastomosis Surgery”.
Risk factors and risk groups	Not available
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4*
Additional pharmacovigilance activities	Not applicable

Missing information Lack of experience in pregnant or lactating women	
Evidence for linking the risk to the medicine	The safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Cumulatively, there have been only one non-serious case with TachoSil use during pregnancy or lactation reported during clinical trials and 4 serious cases containing 5 events (3 serious and 2 non-serious) of exposure to TachoSil during pregnancy or lactation from post-marketig sources. TachoSil should be administered to pregnant and breastfeeding women only if clearly needed.
Risk factors and risk groups	Not available
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6*
Additional pharmacovigilance activities	Not applicable

Missing information Repeated use of TachoSil	
Evidence for linking the risk to the medicine	Allergic reactions may occur especially if TachoSil is used repeatedly. Cumulatively, 11 cases were reported with 11 hypersensitivity events.

Risk factors and risk groups	Not available
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8* *PL Section 4*
Additional pharmacovigilance activities	Not applicable

Missing information Use in paediatric population	
Evidence for linking the risk to the medicine	A total number of 36 paediatric subjects were from clinical trials. A number of 33 cases of TachoSil use in child/paediatric patients (1 serious and 32 non-serious) were reported from post-marketing sources. Because of limited information from clinical trials and post-marketing sources, there is insufficient information on the long-term outcomes of TachoSil use in paediatric population.
Risk factors and risk groups	Not available
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 5.1* *PL Section 2*
Additional pharmacovigilance activities	Corza proposed an extension of the indication to include paediatric population (children from 1 month of age), which was approved by European Medicines Agency (EMA) on 24 March 2023. In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation safety study (PASS) will be performed: PASS-TachoSil Evaluation (PasTel)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TachoSil.

II.C.2 Other studies in post-authorisation development plan

Corza will perform a non-interventional post-authorisation safety study:
PASS-TachoSil Evaluation (PasTel), in order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population.

Purpose of the study:

Corza proposed an extension of the indication to include paediatric population (children from 1 month of age), which was approved by European Medicines Agency (EMA) on 24 March 2023. In order to improve the safety monitoring of TachoSil and to collect additional safety information in the paediatric population, a non-interventional post-authorisation safety study (PASS) will be performed: PASS-TachoSil Evaluation (PasTel). The study is conducted in order to address the safety concern of missing information in paediatric population.

The main purpose of the observational study is to collect long-term safety data on the use of fibrin sealant TachoSil during surgical procedures in paediatric population and to estimate the frequency of adverse reactions over a period of time, extending beyond TachoSil exposure, in a paediatric population of subjects who have been exposed to TachoSil. The study also aims to generate new data to confirm short-term safety of TachoSil in paediatric patients within proposed indication.

Primary endpoint:

- Evaluation of [redacted] safety, including [redacted] of TachoSil up [redacted] follow-up post-surgery period.

Secondary endpoints:

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

No specific adverse event forms are associated with this RMP

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable