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 TachoSil 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 1month to 18 years for supportive treatment in surgery, for improvement of haemostasis, to promote tissue sealing, for suture support in vascular surgery where standard techniques are insufficient, and for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurological surgery.

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 83 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 44 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, one serious cases with one serious event (PT: Off-label use) evidence of "Lack of Experience in Gastrointestinal Anastomosis Surgery" was retrieved from post-marketing sources.
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 no new case reports of exposure to evidence: TachoSil during pregnancy or lactation, only one non-serious case reported during clinical trials. 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. Because of limited information from clinical trials, there is insufficient information on the use of TachoSil 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	Not applicable

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

No pharmacovigilance studies (planned, ongoing or completed) are associated with this RMP.