

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of TachoSil. For information on changes after approval please refer to module 8.**

### 1. Introduction

The term fibrin sealant denotes a product containing coagulation factors, to be administered topically in order to produce a fibrin clot. Typical fibrin sealant kits consist of at least two components, which are kept separately until allowed to mix in topical application. One of the components usually contains human fibrinogen, as substrate of the clot. Additionally, it may contain as further active substances human factor XIII to stabilise the generated fibrin clot and/or inhibitors of fibrinolysis. The other component contains biologically active thrombin, which will convert the fibrinogen of the first component to fibrin. Fibrin sealant products may also be manufactured from autologous products or combined with further components, such as a collagen sponge, or with medicinal products such as antibiotics.

The intended benefit of the topical fibrin sealant application is to support local haemostasis, or “gluing” together of surfaces of injured tissues in order to obtain adaption or sealing of surfaces, to support sutures, or to improve repair and healing. Fibrin sealants have been used to support local haemostasis in surgical situations where tight tissue sealing is required and the usage of other conventional surgical haemostatic means is not possible. Usage of this type of products is therefore particularly justified in surgical procedures involving parenchymal organs such as liver and lung, and/or where rapid reliable haemostasis is required (i.e. neurosurgery). Thus, the mainstay of fibrin sealant use is in patients who require major surgery or experience major trauma, or require endoscopic procedures to stop bleeding.

The efficacy of fibrin sealant products has to be assessed in studies with objective clinical endpoints. Such studies should be controlled studies, in order to demonstrate that the application of fibrin sealant kits provides measurable benefit in comparison to the spontaneous haemostasis and healing process under standard treatment without fibrin sealant.

TachoSil consists of a collagen sponge, manufactured from horse tendons, coated with human fibrinogen and human thrombin. TachoSil therefore differs from other fibrin sealants described in the Ph. Eur. monograph “Fibrin sealant kit” (01/2002:0903). The Applicant has previously developed two predecessor products of TachoSil: TachoComb and TachoComb H. Both consist of an equine collagen sponge coated with a solid component of fibrin glue. The thrombin of bovine origin in the first product, TachoComb, was replaced by human thrombin in TachoComb H in order to address safety concerns such as neutralising antibody formation and TSE related disorders. Both TachoComb and TachoComb H contain the protease inhibitor aprotinin. This component was subsequently removed in the TachoSil formulation, since preclinical development studies conducted by the Applicant demonstrated no clinical effect of aprotinin on haemostasis.

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 could also activate endogenous factor XIII which covalently crosslinks the fibrin to create a firm and stable network.

TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient.

Specific data have not been obtained on the use of this product in neurosurgery, in vascular surgery or in gastrointestinal anastomoses.

Furthermore, the use of TachoSil for tissue sealing is not supported based on the results of the clinical studies undertaken.

## 2. Quality aspects

### Composition

TachoSil is off-white absorbable sponge coated with human fibrinogen and human thrombin. The coated side is coloured yellow. TachoSil is manufactured in three presentations, which differ in the size of the sponge but not in the composition or concentration of the coating. The thickness is for all presentations 0.5 cm.

The composition is given as follows:

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<b>Name of Ingredient</b>	<b>Unit formula/cm<sup>2</sup> sheet</b>	<b>Function</b>
Collagen sponge from equine tendons	2.1 mg collagen	Carrier
<i>coated with:</i>		
Human fibrinogen preparatio	5.5 mg fibrinogen	Active ingredient
Human thrombin preparation	2.0 I.U. thrombin	Active ingredient
Riboflavine	16.5 µg	Dye
<u>Excipients presented in active ingredient:</u>		
Albumin		
Sodium Chloride		
Sodium Citrate		
L-Arginine-hydrochloride		

The product is packed in a double packaging:

Inner container: deep drawn polystyrene blister covered with paper, PE-peellaquer, moisture permeable, germ-proof

Outer container: aluminium-bonded foil sachet, light- and moisture proof, germ-proof.

A desiccant bag (silicagel) is enclosed in the outer container together with the inner container.

### Active substance

#### *Source material*

The plasma is used as starting material for the manufacture of human fibrinogen and human thrombin. Information on the plasma is provided in a Plasma Master File (PMF) format according to guideline II/5272/94. The PMF is submitted as an appendix to the European Drug Master File (EDMF). The same PMF applies to antithrombin III used during the production of thrombin and fibrinogen as well as albumin used as a stabiliser of fibrinogen.

The plasma is obtained from centres located in Austria, Germany and USA. All centres are inspected regularly; European centres are under supervision of national authorities, FDA licenses centres in USA and in addition the German health authorities regularly inspect them. The quality and delivery requirements comply with current regulations of Ph. Eur., US law, WHO recommendations and recommendations of the Council of Europe. The plasma complies with the Ph. Eur. monograph "plasma for fractionation". Selection and screening of donors is in agreement with current regulations.

Details on epidemiological data are provided in detail. Single donations are tested in accordance with the monograph. All plasma pools are tested in compliance with NfG CPMP/BWP/390/97 (introduction of HCV NAT). A validated Nucleic Acid Amplification Technique (NAT) using Polymerase Chain Reaction (PCR) tests all pools additionally for HBV DNA and HIV-1 RNA as well as for high titers of parvovirus B19 DNA. In addition, testing of fractionation pools for HAV genomic material is performed provided all contributing donations have been pre-screened at the donor sample pool level. Information given for the starting material plasma is detailed and shows compliance to all relevant regulations and documents.

### *Active ingredients*

TachoSil drug product is a combination of two drug substances, human thrombin and human fibrinogen, coated on a collagen sponge. Human thrombin and fibrinogen (containing human albumin as a stabiliser) are manufactured by a raw material supplier. Thrombin and albumin are purified from cryo-poor plasma, fibrinogen is purified from cryoprecipitate. The fibrinogen component complies with the European Pharmacopoeia monograph "Human fibrinogen". The albumin complies with the European Pharmacopoeia monograph "Human Albumin Solution". Information on these substances is provided in the form of an EDMF including an open and a closed part.

Freeze-dried Human Antithrombin (AT III) complies with the European Pharmacopoeia monograph "Human Antithrombin III Concentrate, Freeze-Dried" (Ph. Eur. 01/2002:0878).

Efficient removal/inactivation of enveloped viruses during production of fibrinogen, thrombin, and albumin, is indicated by summarised study results, and additional complete reports from the virus clearance studies concerning Human Thrombin, human fibrinogen, Human Albumin 20 % and human antithrombin are provided in the Active Substance Manufactures Part of the EDMF for Human Fibrinogen (including Human Albumin 20% as stabiliser) and Human Thrombin.

The pasteurisation is the key step for inactivation of human plasma-derived products. Virus inactivation during pasteurisation was demonstrated; additionally the gamma irradiation of the final product further contributes toward the safety against enveloped and non-enveloped viruses including parvoviruses.

## **Purification**

### *Process validation*

The manufacture of human thrombin uses techniques of column chromatography and ammonium sulfate precipitation and adsorption to calcium phosphate to yield the drug substance. During this process prothrombin is converted to thrombin in the presence of high citrate concentrations. The drug substance is formulated and filled into glass vials and lyophilised. Vials are closed under nitrogen atmosphere. The drug substance is controlled by appropriately validated methods. The purification process has been analysed for reproducibility by characterisation of the purity/impurity profile using state-of-the-art methods. Consistency of the composition of the active ingredient has been established. The consistency of production has been demonstrated in the given specification limits. The container closure system is suitable for this product. Stability data support the stability of thrombin over a shelf life of 3 years at 2°C-8°C. The thrombin preparation used for the manufacture of TachoSil may be stored maximum for a period of 30 months prior to use. This is justified because the link to the post collection information on donors and donations is maintained beyond the shelf life of the finished product. The thrombin preparation complies with the Ph. Eur. monograph "Fibrin Sealant Kit" (01/2002:0903).

The manufacture of fibrinogen starts from cryoprecipitate. The purification is mainly based on precipitating techniques in the presence of glycine. Residual prothrombin complex proteins are removed by aluminium hydroxide adsorption. The final bulk is prepared by adding human albumin as stabiliser. After filling the drug substance is lyophilised. The drug substance is controlled by appropriate, validated methods. The purification process has been analysed for reproducibility by characterisation of the purity/impurity profile using state-of-the-art methods. Consistency of the composition of the active ingredient has been established. Batch analysis data support the consistent manufacture of the drug substance within the given specification limits. The container closure system

is suitable for the product. Stability data support a shelf life of 5 years. Nycomed is using only the 2 g presentation Fibrinogen used for the manufacture of TachoSil is batch released by an Official Medicines Control Laboratory (OMCL). The fibrinogen is stored up to a maximum period of 4 years prior to processing into TachoSil. This is justified because the link to the post collection information on donors and donations is maintained beyond the shelf life of the finished product TachoSil. This fibrinogen component complies with the Ph. Eur. monograph “Human Fibrinogen”.

### **Other ingredients**

Albumin is used as excipient (stabiliser) in the manufacture of fibrinogen. The purification follows the Cohn fractionation process. The drug substance is pasteurised two times: first, in a steel tank before filling and second, in the glass container after filling and closing. Consistency of the manufacture and composition of albumin with regard to the purity/impurity profile has been established. The albumin used for TachoSil is licensed in some EU member states. For the manufacture of fibrinogen for TachoSil Human Albumin presentations of 50 mL and 100 mL are used. It is batch released by an OMCL. The albumin is used as stabiliser for the manufacture of fibrinogen up to eight months from the date of release. Human Albumin 20% complies with Ph. Eur. monograph “Human albumin solution” (Ph. Eur. 01/2002:0255).

During some manufacturing steps of thrombin and fibrinogen, antithrombin III, which itself is a blood product, is added, but removed during the manufacturing process. Only antithrombin, which has undergone the Official Medicines Control Laboratory (OMCL) Batch Release Procedure, is used. Details on the manufacture, virus safety and specifications of this product have been provided and are acceptable.

For collagen there exist no monograph. Nycomed manufactures the collagen from horse tendons. Analytical methods have been validated and the consistency of production has been demonstrated by in-process controls from three batches as well as batch release testing results from these batches. Specifications are acceptable. The microbial purity has been limited to 100 CFU/45cm<sup>2</sup> before irradiation, and assuming an average weight of 100 mg of one sheet this corresponds to the 1000 cfu/g, which is given in the collagen specification. The shelf life of the collagen sponge before use in TachoSil is limited to 1 year, which is justified, based on the stability data.

### **Specifications**

The specifications for the actives substances have been set. Testing instruction for all analytical methods is provided. The methods are properly validated. The tests are suitable for the control of the drug substances, thrombin and fibrinogen. There are no concerns regarding the control of the drug substances for TachoSil.

### **Product development and finished product**

#### *Product development*

For the manufacture of TachoSil a mixture containing the drug substances thrombin and fibrinogen is coated on collagen sponges using a dripping device. The coated sponges are cut into sheets, dried and transferred to a contract manufacturer for primary packaging. After shipment to another contract manufacturer, the medicinal product is sterilised by gamma irradiation. Nycomed, Austria performs final packaging.

#### *Manufacturing process*

The main steps of the TachoSil manufacture are carried out at:  
Nycomed Austria GmbH, St. Peter Straße 25, A-4020 Linz, Austria.

Primary/Secondary packing is carried out at the following location:  
Steripac GmbH, Oberreichenbacher Strasse 17, D-75365 Calw Altburg

Sterilisation by gamma irradiation is carried out at the following location:

Rüsch Sterilisation Service GmbH, Willy Rüsch Str. 4-10, D-71394 Kernen-Rommelshausen, Germany.

Flow chart of the whole manufacturing process is provided in the dossier.

#### *Finished product specification*

The specifications are based on the manufacture of the predecessor products, TachoComb and TachoComb H, which is very similar to the production of TachoSil

The specific limits are considered to be adequate due to the fact that the active ingredients are of biological origin.

In-process controls in TachoSil manufacture before packaging and irradiation are provided.

Release and shelf life specifications for 3 sizes of TachoSil are provided.

#### *Control of excipients*

Collagen sponge: Method validation is provided. Consistency of manufacture is shown by analytical data from 3 production and validation runs and all parameters comply with the specifications.

The quality and testing of the excipients conforms to the respective Ph. Eur. Monograph.

#### *Stability data*

There are two crucial steps during the manufacture of TachoComb. These are: first, the stability and suitability of the coating suspension for the intended purpose and second, the stability of thrombin during gamma irradiation. Conditions for the coating solution must be controlled because thrombin must be kept inactive thus avoiding the cleavage of fibrinogen to fibrin and on the other hand conditions must also lead to an appropriate adhesion of the coating mixture. Appropriate development studies have been performed and in-process controls have been implemented which control this critical step. Development studies on the stability and homogeneity of the coating suspension with regard to thrombin and fibrinogen during the whole manufacturing process have been provided. These data justify an overage of thrombin at the beginning of the process. Especially the influence of the sterilisation procedure by gamma irradiation, which is justified according to Note for Guidance CPMP/QWP/054/98 corr, has been analysed. The sterilisation procedure has been validated following the NfG "The use of ionising radiation in the manufacture of medicinal products" (III/9109/90). The analytical methods for the control of the drug product are validated. Results from batch release testing support the view of a consistent manufacture of the product thus leading to the conclusion that the production is under good control. The specification limits of the active substances fibrinogen and thrombin have been reconsidered and reflect the current experience of manufacture of TachoSil and the results of batches used for clinical studies. Nycomed has committed to re-consider the data again on the basis of 20 batches. The necessity of broader shelf life specifications is accepted. Stability data for normal size TachoSil at temperatures of 2-8°C, 25°C and 30° are available for a period of 3 years and data at 40°C for a period of 6 months. All results are within specification limits. Additional data are presented for the midi (1 batch) and mini size (3 batches) presentations, which have been stored under the above, mentioned temperature conditions for 6 months. All data are within specifications. A shelf life of 3 years at room temperature should be granted.

Primary packaging and secondary packaging have been shown to be suitable for the production (irradiation sterilisation) and storage of the product.

#### **TSE safety**

TachoSil consists of human plasma derived proteins coated on a collagen fleece, which are derived from horse tendons. No substances, which fall under the scope of the TSE Guideline, were identified. The supplier of the active raw materials for products has provided declarations to this effect: Human Fibrinogen, Human Albumin, Human Thrombin and Antithrombin.

#### **Viral safety**

The TachoSil production process has been sufficiently investigated on its capacity to remove/inactivate viruses. It should be further considered that the final gamma irradiation is also effective against potential contaminants from human plasma proteins (thrombin, fibrinogen, albumin).

There is a sufficient safety margin for enveloped viruses such as HIV, HBV, and HCV while the risk for HAV and B19V-infection has been minimised by several measures including NAT-screening and virus inactivation/removal steps during production. In addition, the gamma irradiation of the final product further contributes towards the safety against enveloped and non-enveloped viruses including parvoviruses.

Potential viral contaminants from equine tendons used as starting materials of the collagen fleece are subjected to two steps with capacity for virus inactivation: acid treatment and gamma irradiation. Both steps are effective for inactivation of enveloped viruses. The final gamma-irradiation step is effective against a broad range of viruses. Enveloped and non-enveloped viruses with large genomes are effectively inactivated and a moderate inactivation capacity (ca. 3 log<sub>10</sub>) for inactivation of viruses with very small genomes (Parvoviruses) was determined. In conclusion, the virus safety of TachoSil is acceptable.

### **Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CPMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

### **3. Non-clinical aspects**

#### **GLP**

Pivotal toxicity studies with TachoComb H were performed in compliance with the OECD Guidelines for Good Laboratory Practice (GLP). Studies on general pharmacodynamic effects were not performed under GLP conditions since this is not required by EU Guidelines.

#### **Pharmacology**

##### **Primary pharmacodynamics**

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 presence of physiological saline, the solid components of the coating dissolve and the subsequent fibrinogen-thrombin reaction initiates the last step of blood coagulation. Fibrinogen is converted into fibrin monomers, which spontaneously polymerise to a fibrin clot, then crosslinked by endogenous factor XIII, to create a firm, mechanically stable network.

The need of aprotinin as a constituent of topical haemostatic and tissue sealing medicinal products was examined under normal, stressful and hyperfibrinolytic conditions. It was concluded that TachoSil without aprotinin is an effective haemostatic and tissue sealing product and as effective as TachoComb with aprotinin even under severe hyperfibrinolytic conditions.

*Normal condition:* A comparison of TachoComb H and TachoSil in sealing spleen- and liver lesions in dogs was performed. Gross observation during surgery and at 48 hours post-surgery and histopathological figures showed no differences with and without aprotinin. There were no re-bleedings and both medicinal preparations showed full pharmacological efficacy.

*Stressful conditions:* TachoComb H was compared to TachoSil in a pig spleen lesion model under extremely elevated intrasplenic pressure. The histopathological results demonstrated a slightly more pronounced degradation of the fibrin clot without aprotinin, however, haemostatic and sealing effects

were maintained. It was concluded that TachoSil is as effective as TachoComb H in terms of haemostasis and tissue sealing.

*Hyperfibrinolytic conditions:* TachoSil and TachoComb H were studied in a pig pancreatitis model. The medicinal preparations were applied to lesions on pancreas and spleen. After 72 hr, the short term behavior and resistance to enzymatic degradation were investigated by increasing the intrasplenic pressure. TachoSil resisted the same increased intra-organ pressure as compared to TachoComb H. The haemostatic and sealing efficacy of TachoSil was not influenced under these severe hyperfibrinolytic conditions.

A second hyperfibrinolytic condition was achieved by local administration of r-tPA before applying TachoSil or TachoComb H to cortical brain lesions in rabbits. The haemostatic and tissue-sealing efficacy of TachoComb H and TachoSil was examined after topical administration to experimental cortical brain lesions in rabbits both with and without plasminogen activator. No differences were obtained in efficacy between TachoSil and TachoComb H despite the fact of severe haemorrhage.

Dose range finding studies in rat liver and kidney models were performed using both TachoSil samples containing constant fibrinogen and varying thrombin concentrations and TachoSil samples containing constant thrombin and varying fibrinogen concentrations. The results confirmed the already selected optimal dose of fibrinogen and thrombin in TachoComb and TachoComb H.

Moreover, evaluation of tissue adherence of TachoComb, TachoComb H and TachoSil to pleural porcine tissue did not reveal significant differences if the pressure of detachment was determined.

A comparison of TachoComb H and TachoSil was conducted in sealing spleen- and liver lesions in dogs. The obtained results showed no differences between the two medicinal preparations concerning efficacy at gross observation during surgery, at autopsy 48 hours post surgery and histopathology. Not any case of secondary haemorrhage, change in blood count and coagulation tests was revealed.

### **Secondary pharmacodynamics**

Secondary pharmacodynamics is discussed together with safety pharmacology below.

### **Safety pharmacology**

Safety pharmacology is based on previously obtained data with TachoComb containing equine collagen, human fibrinogen, bovine thrombin and bovine aprotinin. An extensive safety pharmacology programme was carried out with TachoComb in rats, guinea pigs and dogs. The fleece was administered into the abdominal cavity via laparotomy (fourfold to fifty fold of the clinical dose) and compared with sham-operated control animals. As control substances Avitene (microfibrillar collagen hemostat) and collagen sponges (Nycomed) were used. The main components of the coating, fibrinogen, bovine thrombin and aprotinin were examined in isolated organ experiments (guinea pig ileum, rat uterus). General pharmacodynamics effects were negligible or mild, if any. No changes were caused in general behavior (rat), pain sensitization (rat), spontaneous motor activity (rat), sodium pentobarbital-induced sleeping time (rat), induced convulsions (rat), body temperature (rat), respiratory and cardiovascular systems (dog), fibrinolysis/coagulation (rat), and gastrointestinal transit (rat). There was no or only a mild influence on isolated organs not of toxicological relevance for the human patient with TachoComb. Other effects studied without showing an influence of TachoComb include urinary volume and electrolyte excretion in rats and effects on coagulation and fibrinolysis in rats. In conclusion, TachoComb did not show limiting side effects in these *in vivo* and *in vitro* general pharmacodynamic studies. In view of the composition of TachoSil and given the fact that the medicinal product is for topical use only, repeated investigations with reference to safety pharmacology are considered of limited value.

### **Pharmacodynamic drug interactions**

Pharmacodynamic drug interactions between topically administered TachoSil and other drugs are essentially absent. Nevertheless, drugs co-administered systemically or topically may affect the haemostatic and tissue sealing properties of TachoSil. Previous studies with TachoComb in rats pretreated with warfarin or heparin showed that the haemostatic and tissue sealing properties of TachoComb are preserved even under severe disturbances of the blood clotting. Similarly, the function of TachoSil was preserved if r-tPA was topically co-administered. On the other hand, absorbed active components of TachoSil, fibrinogen and thrombin, might influence the equilibrium between the blood

clotting and fibrinolytic system. However, due to the protein nature of both components, absorption of intact fibrin and thrombin in pharmacologically relevant amounts should not occur.

## Pharmacokinetics

### *Absorption- Bioavailability*

In a study in rats the decrease of labelled fibrinogen was determined at the site of application for TachoComb, i.e. wounded liver. The appearance of radioactivity within the rat liver tissue exposed to <sup>125</sup>I-fibrinogen of TachoComb probably demonstrated absorption of degradation products directly by liver tissue. The radioactivity concentration at the application site decreased from 39.08 µg eq. of fibrinogen/g at 6 hours after administration to 2.56 µg eq./g at 336 hours (=14 days) after administration. The plasma concentration measured 6 hours after application (7.78 µg eq./ml) declined to 0.12-µg eq./ml after 336 hours.

In another study in rats TachoComb was applied to a liver wound and the time until the disappearance of the tested substance was measured; autopsies were performed at 2, 4, 8, 12, 16, and 20 weeks. In a group treated with 0.5 x 0.5 cm/animal, TachoComb had disappeared after 10 - 20 weeks, while it had disappeared after 12 - 16 weeks in a group treated with 1.0 x 1.0 cm/animal and 1.5 x 1.5 cm/animal.

Schelling et al. investigated the haemostatic properties of TachoComb in experimental lesions of the liver, spleen and arterial vessels. As part of their study, they reported on the post-operative degradation processes and the changes in tissue structure. Macroscopically, only minimal tissue reactions were found, which were strictly confined to the area that had been covered with TachoComb. By the 14<sup>th</sup> postoperative day, histological examination showed unspecific fibrovascular granulation tissue containing fibroblasts, neutrophils, lymphocytes and only a few giant cells, which are indicative of a foreign-body reaction. After four weeks the histological picture showed progressive absorption. While TachoComb was still recognizable, it had been considerably reduced and partly replaced with cell-free connective tissue.

### *Distribution*

The distribution of labelled <sup>125</sup>I-fibrinogen was investigated after administration of TachoComb via laparotomy to a wound of the liver in male rats. Groups of rats were killed at 6 hours, 24 hours, 3 days, 7 days and 14 days after treatment. In all tissues, except for the thyroid gland, the radioactivity concentration showed a maximum value at 6 hours after application. At this point in time, concentrations higher than that measured in the plasma (max 7.78 µg eq./ml) were only found in the thyroid gland (97.86 µg eq./ml) and at the application site of the liver. In other tissues, the concentration was similar to that measured in the plasma, or lower. At 336 hours (14 days) after application, the concentration in the thyroid gland had decreased to 17% of the maximum value. In the brain, thymus gland, suprarenal glands and skeletal muscle, the concentration had sunk beyond the detection limit. In the other tissues, the concentration had decreased to 1 - 8% of the maximum value.

### *Metabolism*

The coated collagen fleece and similar products like fibrin adhesives are physiologically degraded and replaced by tissue via two metabolic mechanisms: (1) The collagen fleece is degraded layer by layer by absorptive granulation tissue and converted into a pseudo-capsule consisting of endogenous connective tissue; (2) The lysis of the clotted coating is comparable to that of the endogenous fibrin by fibrinolysis and phagocytosis. The degradation time of the resultant fibrin depends on its volume and on the reactivity and fibrinolytic potency of the surrounding tissue. The activation of the fibrinolytic system, i.e. conversion of the proenzyme plasminogen into plasmin, is a proteolytic process whereby sensitive bonds in the plasminogen molecule are cleaved. The *in vivo* activation is carried out by special activators, proteolytic enzymes, which cause specific cleavage in plasminogen, which results in its conversion into the proteolytic enzyme. The fibrin degradation products formed during breakdown are removed like in endogenous degradation, i.e. by elimination via the reticulo-endothelial system.

The degradation of TachoComb H via metabolism was examined in dogs after single administration to a liver wound after laparotomy. The animals were observed for 2, 4, 6, 12 and 24 weeks after surgery. After 2 weeks compound remnant was approximately half the size of the TachoComb H. The amount of compound remnant decreased with time. Only few spots were present at week 24. During degradation the product is replaced by endogenous tissue.



In rats administered TachoComb on liver wounds, the time to disappearance was measured during 2-20 weeks. The degradation time of the fleece was between 16 and 20 weeks.

#### *Excretion*

Excretion and recovery of radioactivity was determined after administration of 125-I-fibrinogen with TachoComb. As late as 504 hours (21 days) after application, 89.3% of the dose (radioactivity) had been excreted in the urine, and 3.9% had been excreted in the faeces. At this point of time, 0.4% of the dose was found in the thyroid gland, and 6.4% in the organism.

#### *Pharmacokinetic drug interactions*

Studies on pharmacokinetic drug interactions were not performed.

### **Toxicology**

TachoSil differs from TachoComb H only in lacking the bovine aprotinin. The results obtained with the predecessor products, specifically with TachoComb H, are thus considered relevant.

#### **Single dose toxicity**

No single dose toxicity studies have been performed with TachoSil, but reference is made to studies with the predecessor products. Four acute toxicity studies were conducted in rats and dogs after insertion of TachoComb H, TachoComb and Tachotop into the peritoneal cavity via laparotomy. One additional safety study was performed with TachoComb H in dogs.

The doses administered i.p. to rats and dogs for evaluation of single dose toxicity of the medicinal preparations ranged from 10 mg/kg to 1000 mg/kg bw (rats) and 5-500 mg/kg (dogs), i.e. about 50 – 200 times the clinical dose for humans.

No deaths occurred. There were no effects of toxicological importance on body weight, food consumption, haematology, blood clotting, blood chemistry, and organ weights, which could be attributed to TachoComb preparations tested. There were no gross post mortem or histopathological findings of toxicological importance that were considered to be an effect of intraperitoneal insertion of TachoComb preparations.

In *dogs*, TachoComb H was generally well tolerated up to the highest dose level tested in single dose toxicity study (500 mg/kg). Insertion of the fleeces was followed by observation periods of two weeks for all groups, and of four weeks for additional animals at the 500-mg/kg-body weight dose level and sham-operated control group. There were neither mortalities nor other major toxic findings on body weight, general appearance, clinical pathology (haematology, clinical chemistry and coagulation), autopsy, and histopathology. The non-toxic-effect level of TachoComb H in dogs was 500-mg/kg body weight. In *rats*, the observed maximum non-lethal dose was 1000 mg/kg.

#### **Repeat dose toxicity**

No repeat dose toxicity studies have been performed with TachoSil. TachoSil is not intended for repeated applications over a long period of time, thus routine repeated dose toxicity studies do not seem to be relevant for risk assessment. Nevertheless, one 4-week study has been performed with TachoComb. The fleece was inserted by laparotomy into the abdominal cavity of rats 5, 50 or 500 mg/kg of once weekly for a total of 4 doses, followed by autopsies 1 or 4 weeks after the last administration. Essentially no adverse effects were seen at doses up to 50 mg/kg. At the 500-mg/kg-dose level, there were slight effects on food and water intake. Locally, there were dose-related adhesions of the fleeces with the operated site or intraperitoneal organs associated with inflammation. No other effects on general health or on other parameters attributable to the medication were observed in this series of experiments.

#### **Reproductive and developmental studies/ Genotoxicity/ Carcinogenicity**

No studies regarding the effect on reproduction and carcinogenicity have been performed with TachoSil. TachoSil is a medication intended to be used during surgical intervention and will usually be applied only *once* per patient. Regular repeated administration is not expected. None of the components of TachoSil is known to have an effect on reproduction or to possess mutagenic or carcinogenic potential. Furthermore, as the main components of TachoSil are heterologous proteins for animals, no useful results are expected from reproduction or carcinogenicity studies.

### **Local tolerance**

No separate studies on local tolerance were undertaken with TachoSil, but local tolerance was investigated as part of the pharmacodynamic trials. TachoSil as well as its predecessors were applied to different organs and tissues, i.e. brain, liver and spleen. Specific local reactions were largely absent. Inflammatory-like reactions were observed, but more likely due to mechanical irrigation and were not regarded as toxic.

Further, one of the predecessors, i.e. TachoComb H, was investigated in dogs over six months following a single insertion to liver wounds. The treated group received a single dose of 2 cm<sup>2</sup> TachoComb H/kg, equivalent to the use of 2-3 patches of TachoComb in a human. Two weeks after surgery, the compound remnant covered an area of liver capsule approximately half the size of the TachoComb H applied originally. Only few spots of compound remnant were present without signs of local irritation 24 weeks after surgery representing the expected degradation of the fleece. There were no signs of local intolerance. There were no histopathological findings attributable to intraperitoneal application of TachoComb H. No parenchymal damage was observed.

### **Antigenicity**

The risk of possible antigenicity was investigated in rats and guinea pigs with TachoComb, Tachotop, as well as irradiated and non-irradiated single components human fibrinogen, human thrombin and equine collagen. TachoComb was found to be immunogenic in guinea pigs after repeated subcutaneous administrations. However, positive reactions were caused only by human fibrinogen.

### **Studies on impurities**

Based on toxicity studies possible toxicity of the excipient collagen can be ruled out. The other excipients (Human Albumin, L-Arginine Monohydrochloride, Sodium Chloride, Trisodium Citrate, Riboflavine (E 101) to mark the coated side) are well known substances and no incompatibilities are to be expected.

### **Ecotoxicity/environmental risk assessment**

The toxicity data of this product and its single components do not provide any risk for the environment.

### **Discussion on the non-clinical aspects**

The amount and the quality of pharmacodynamic investigations are considered sufficient, based on several studies showing TachoSil to be effective in haemostasis and tissue sealing in different animal models. The efficacy of TachoSil was studied under normal, stressful and hyperfibrinolytic conditions. A number of species including dog, pig and rabbit were studied and a number of organs investigated including spleen, liver, pancreas and brain. The results confirmed that the absence of aprotinin did not affect the therapeutic properties of TachoSil. Of note, one study revealed a slightly more pronounced degradation of the fibrin clot after application of TachoSil (without aprotinin) compared to TachoComb H (with aprotinin). However, this should not influence the efficacy of TachoSil at least not in the time-window of interest.

Investigations concerning secondary and safety pharmacology have not been performed with TachoSil, but the Applicant refers to studies performed with the predecessor TachoComb. These studies revealed no findings of clinical significance. In view of the composition of TachoSil and given that the product is intended only for topical use, investigations concerning safety pharmacology are not considered necessary and should not be repeated with TachoSil.

Pharmacodynamic drug interactions between TachoSil and other drugs have only been investigated in one study with r-tPA. However, interactions between topically administered TachoSil and other drugs are not considered as important as they are for other drug substances. Nevertheless, the Applicant will put particular focus on potential drug interactions, especially with other anticoagulants, during the post-marketing activities and as part of a safety surveillance study.

No pharmacokinetic studies were performed with TachoSil, but the Applicant refers to studies performed with the predecessor TachoComb and TachoComb H. In view of the intended use of TachoSil, the most relevant pharmacokinetic properties pertain to time course of degradation

("absorption") under *in vivo* conditions. The disappearance of the implanted medicinal product from the site of application and of their labelled compounds (125-I-fibrinogen) during distinct time periods may be considered as indicative of absorption and metabolism. *In vivo* investigations to study the disintegration of coated collagen sheets were performed with TachoComb implanted in the peritoneal cavity. The degradation process of bovine thrombin should not differ considerably from that of human thrombin. Further, aprotinin that is an inhibitor of proteolytic enzymes, is absent in TachoSil. Consequently, an accelerated degradation may be suggested with TachoSil in comparison to other TachoComb preparations with aprotinin. As the pharmacodynamic properties remain comparable between the TachoComb preparations with and without aprotinin (*see section on pharmacodynamics*), a potentially faster degradation of TachoSil is of subordinate relevance. After application of 125-I-(fibrinogen)-TachoComb and absorption from the application site, accumulation of radioactivity in the thyroid gland, but not in other organs and tissues was observed. This finding indicates the well-known problem of *in vivo* deiodination.

Overall, the limited pharmacokinetic test programme is considered acceptable, as the compounds of TachoSil are endogenous and thus are expected to follow the usual pathways for metabolism and excretion of proteins. Degradation and replacement occur via two mechanisms: the fibrin clot is degraded partly by fibrinolysis and partly by cellular phagocytosis, while the collagen patch is degraded layer by layer by absorptive granulation tissue and converted into a pseudo-capsule consisting of endogenous connective tissue ("scar"-formation).

Since the components of TachoSil are endogenous compounds, it is appropriate that there are no studies of protein binding, metabolic pathways and possible interaction with the cytochrome P450 system.

Both active ingredients are present in the active layer of TachoSil in a dry, solid stage and thrombin reacts with fibrinogen to form the fibrin clot immediately after moistening of TachoSil. This was indirectly proven with the predecessor product TachoComb by means of investigating the adhesive strength of TachoComb in a plate adhesion test. TachoSil must be moistened to exert its effects also in clinical settings and it is therefore highly unlikely that enough excess thrombin for systemic uptake would be available. It can further be expected that protease inhibitors present in the blood would inactivate an excess of thrombin. Moreover, during surgical settings, it is unlikely that thrombin would be uptaken against the blood stream. Furthermore, in case of systemic uptake of thrombin the blood coagulation parameters would be influenced. Toxicology studies performed with TachoComb H revealed no relevant changes in blood coagulation parameters, not even if the product was in contact with a bleeding liver wound. Likewise, no changes in blood coagulation parameters were reported in the clinical trials performed with TachoSil nor during the decade of clinical experience with approximately 700.000 patients treated with the predecessor products so far. However, the Applicant will put particular focus on the issue of thromboembolic potential post-marketing through the usual pharmacovigilance reporting tools and as part of a safety surveillance study.

No single dose toxicity studies have been performed with TachoSil, but the Applicant referred to studies performed with the predecessor products. Five acute toxicity studies were conducted in rats and dogs with TachoComb H, TachoComb and Tachotop. The presented data indicate a good safety profile of TachoComb preparations in rats and dogs, even after i.p. administration of doses 100-200 fold of those indicated for humans. No repeat dose toxicity studies have been performed with TachoSil. One 4-week study has been performed with TachoComb and essentially no adverse effects were seen at doses up to 50 mg/kg.

Based on the provided data upon the predecessor products and in view of the composition of TachoSil, it is agreed that new acute or repeat toxicity studies are not considered necessary.

No studies regarding the effect on reproduction, mutagenicity and carcinogenicity have been performed with TachoSil. Again, such studies are not considered relevant in view of the composition of TachoSil and the intended use, i.e. single application.

Further, toxicological investigations with reference to local tolerance, antigenicity and studies on impurities, did not reveal any concerns in view of the safety of TachoSil. Furthermore, the risk of possible antigenicity of TachoSil is considered low in view of the composition of TachoSil. It is

assumed that human fibrinogen is not antigenic in humans as it is a homologous protein. Adverse reactions due to possible immunogenic defence reactions should therefore essentially not occur in humans, even after repeated administration of TachoSil. Moreover, TachoSil is not intended for regular repeated administration to humans and will usually only be applied once per patient.

Induction of cell-mediated or humoral response by equine collagen could be provoked only by use of an adjuvant. The equine collagen component of TachoSil is not expected to induce an immunological response under clinical conditions. Nevertheless, the Applicant has made a commitment to put particular focus on immunogenicity during the post-marketing activities and as part of a safety surveillance study.

In conclusion, the assessment of non-clinical data indicates an acceptable safety profile of TachoSil.

#### **4. Clinical aspects**

##### **GCP**

The Applicant claims that both pivotal TachoSil trials (TC-013-IN and TC-014-IN) and the additional study (TC-016-IN) have been performed according to the ethical principles of the declaration of Helsinki and in accordance with local requirements as well as in accordance to Good Clinical Practice. The trials have been audited and certified for GCP.

#### **CLINICAL PHARMACOLOGY**

##### **Pharmacokinetics**

No pharmacokinetic studies have been performed in humans.

In view of the intended topical use of the product, which is largely independent from intrinsic and extrinsic factors, metabolism – in the sense of absorption or degradation – remains the only relevant pharmacokinetic parameter to be discussed.

Homologous fibrinogen and thrombin as well as the resulting fibrin clot, but also the sponge from equine collagen, are expected to be metabolised in the same way as the patient's own respective compounds. Indeed, animal studies with the predecessor products of TachoSil confirmed that i) the clotted coating is metabolised by fibrinolysis and phagocytosis and ii) the collagen sponge is progressively degraded layer by layer by absorptive granulation tissue and converted into a pseudocapsule consisting of connective tissue. Depending on the size of the experimental wound covered as well as the organ system and the species of animals investigated, only few remnants of the collagen sponge were present after approximately 24 weeks, without any signs of irritation (see Non-Clinical part).

##### **Pharmacodynamics**

No specific primary or secondary pharmacodynamic studies have been performed in humans.

In a series of preclinical investigations in animals, TachoSil demonstrated haemostatic efficacy, adhesion to the wound surface and airtight sealing properties, in a variety of different models *in vivo* and *ex vivo* (see Non-Clinical part). However, in these studies, pharmacodynamics was not investigated directly but via indirect parameters such as time to haemostasis. To directly investigate the pharmacodynamic properties of TachoSil, the ability, the speed and the stability of clot and tissue sealing should have been studied. However, there are no methods or parameters available for such studies and information on human pharmacodynamics was therefore gathered as part of the clinical studies.

##### *Mechanism of action*

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 presence of physiological saline, the solid components of the coating dissolve and the subsequent fibrinogen-thrombin reaction initiates the last step of blood coagulation. Fibrinogen is converted into fibrin monomers, which spontaneously polymerise to a fibrin clot, then crosslinked by endogenous factor XIII, to create a firm, mechanically stable network.

### *Pharmacodynamic drug interactions*

Studies on pharmacodynamic drug interactions were not undertaken.

## **Clinical efficacy**

### **Introduction**

The clinical efficacy of TachoSil in supporting haemostasis and tissue sealing was investigated in two pivotal trials. One study was conducted in sealing of air leakages during lung surgery (TC-013-IN) and one in patients undergoing partial liver resection (TC-014-IN). No clinical experience with TachoSil was available prior to conducting these trials. The Applicant submits five clinical trials with TachoComb H as additional supportive evidence. These are Phase III studies PHTC 009, PHTC 008, PHTC 007, PHTC 006 and TC-011 AU. These studies are submitted in view of the pre-clinical evidence of similarity between the final product and its predecessor.

Due to the nature of the product both pivotal trials with TachoSil and similarly all the trials with TachoComb H were conducted in an open, randomised, prospective and multicentre fashion. The choice of active comparator in the pivotal studies TC-013 IN and TC-014 IN as well as in the additional study TC-016 IN (and in all but one of the supportive studies) is standard surgical management with sutures and argon beamer, respectively. Except for one trial with TachoComb H, i.e. a study on lymphatic sealing (TC-011-AU), a patient population being equally eligible for treatment with TachoSil/ TachoComb H and surgical standard techniques was selected and then randomised to receive either the test product or standard therapy. In contrast, the lymph study investigated the efficacy of TachoComb H in addition to surgical standard compared to surgical standard alone, in a randomised, open manner. Patient populations were selected by surgical condition and randomised to receive either TachoSil or treatment according to surgical standard, with the aim of demonstrating superiority of TachoSil over active standard therapy.

The patients enrolled in all the trials submitted were above 18 years of age, no upper limits were defined for the two pivotal trials, and for study PHTC 009. Trials PHTC 006/008 and TC-011-AU did not include patient beyond the age of 85 and 80 years, respectively.

The Applicant is currently conducting a further confirmatory clinical trial with TachoSil in renal surgery, TC-015-IN. The results of this study will be communicated to the CPMP as a post-marketing commitment.

The amount of product used in the trials was individualised by the treating surgeon with the exception of supportive study TC-011 AU. All of the TachoSil and TachoComb H sponges provided for clinical trials measured 9.5 cm x 4.8 cm and were 0.5 cm thick.

### **Overview of Clinical Efficacy and Safety Programme**

<b>Trial</b>	<b>Type of Surgery</b>	<b>N. of Subjects</b>
<u>Pivotal Trials (TachoSil)</u>		
TC-013 IN	Pulmonary	189 (C=93)
TC-014 IN	Liver	121 (C=62)
TC-016 IN	Liver	119 (C=60)
<u>Supportive Trials (TachoComb H)</u>		
PHTC 009	Liver	292 (C=97 and 96)
PHTC 008	Vascular	24 (C=12)
PHTC 007	Pulmonary	92 (C=46)
PHTC 006	Vascular	60 (C=30)
TC-011 AU	Lymphatic	61 (C=31)

## **Dose response studies**

No designated dose response studies were performed with TachoSil. According to the Applicant, the dosing recommendation is based on preclinical findings and on clinical experience with both TachoSil and predecessor products, and this development reflects the nature of the product. However, the sponges used in all clinical trials measured 9.5cm x 4.8 cm and were 0.5 cm thick, no further specific clinical data are made available in the dossier in support of the proposed dosage and administration.

The optimal dose is predefined as an amount of Fibrinogen and Thrombin per cm<sup>2</sup> of TachoSil fleece material. However, the amount of TachoSil used by the surgeon cannot be pre-defined as the amount (dose) needed depends on a case by case clinical judgement by the surgeon, primarily based on the size of area needing treatment by TachoSil, i.e. as defined in protocols: TachoSil must cover any resection site at least 1 cm beyond its margins. If several patches are required these must overlap.

**Main studies** (Studies TC-013-IN, TC-014-IN, TC-016-IN)

### **Study TC-013-IN**

An open, randomised, prospective, multicenter, parallel-group phase III trial to compare the efficacy and safety of TachoSil vs standard surgical treatment (SST) in patients undergoing lobectomy for lung cancer and requiring treatment for air leakage after primary stapling.

### **Methods**

#### **Study participants**

Patients aged 18 or above with air leakage grade 0, 1 or 2 who were planned to undergo elective lobectomy with or without lymphadenectomy for lung cancer with antero- or postero-lateral incision were to be included in this trial.

#### **Treatments**

TachoSil was applied to all resection surfaces, specifically the hilar area, regardless of the degree of air leakage present at randomisation. The number of TachoSil sponges to be applied was not prespecified in the trial protocol but depended on the patient's individual size of the bleeding or leaking wound surface, which had to be covered in total.

In the comparator group, patients presenting without air leakage received either no further treatment or additional suturing at the hilar part of the resection area, according to the discretion of the surgeon, whereas patients with mild to moderate air leakage were subjected to standard management with sutures, according to the routine of the centre.

#### **Outcomes/endpoints**

##### *Primary endpoint:*

- Incidence of air leakage 42-54 hours after surgery

Air leakage was assessed on day 1, the day of the operation, using the water submersion test (grades 0-3). Two assessments were made, immediately after surgery (baseline) and after the first use of study treatment. Patients with grade 3 immediately after the operation had continued surgery until grade 0, 1 or 2 was obtained.

On days 2-9 air leakage was assessed once daily using the Pleur-Evac (grades 0-7). In both tests low grades represent less air leakage with grade 0 signifying no leakage.

##### *Secondary endpoints:*

- Reduction of intra-operative air leakage intensity after the first test treatment;
- Intensity and duration of post-operative air leakage;
- Duration of post-operative chest tube drainage up to 9 days after surgery.

### Sample size

It was planned that 200 patients should be recruited into the study in a 1:1 randomisation. The randomisation was stratified according to the grade of air leakage at baseline, grade 0 or grade 1-2. However, recruitment was halted when only 189 patients were recruited. The reason given for the early stopping was a slower than expected recruitment rate. It was calculated that with 200 patients the expected power was 87%, whereas 189 patients still gave 85% so it was considered acceptable to stop recruitment.

### Statistical methods

The ITT population was defined as the primary population. This is appropriate as the aim of the trial is to establish superiority over the comparator. The population was defined as all patients randomised and given treatment. This is not an appropriate definition for the ITT population in an open-label trial, and all randomised patients should have been included, but as there were no patients who were randomised and not treated this is not an issue.

	TachoSil	Standard
ITT population	96	93
Baseline grade 0	50 (52%)	50 (54%)
Baseline grade 1-2	46 (48%)	43 (46%)

There was a large baseline imbalance in the area of the treatment site. The large amount of missing data for this variable in the standard group is surprising and may have something to do with the apparent imbalance. Alternatively there may have been a problem with the randomisation in this open study, the result being that more severe patients were more likely to receive the active treatment. This is possible as patients were not randomised until after the baseline air leakage had been assessed. If this were the case the implications for interpreting the data from the study would be serious.

Area of first treatment site of the lung (cm<sup>2</sup>)

	N	Mean (SD)	Median
TachoSil	96	19.75 (14.33)	25.13
Standard	71	8.04 (7.91)	6.28

All statistical tests were to be performed using a type I error (two-sided) of 0.05. With respect to the primary endpoint, the incidence of air leakage 48 ± 6 hours after completion of surgery, both treatment groups were compared by means of a two-sided Fisher test. This was done for the ITT as well as the PP population. Additional analyses by means of Cochran-Mantel-Haenszel tests were performed to account for the centres and strata at randomisation respectively.

Duration of post-operative air leakage and post-operative chest tube drainage respectively was compared between both treatment groups using a log-rank test stratified for centre.

In general, missing values were not substituted except for the AUC of the post-operative intensity of air leakage where missing values were replaced by zero.

Demographics, pulmonary function, operation and test treatment variables as well as chest X-ray findings were tabulated, only.

### Study TC-014-IN

An open, randomised, prospective, multicenter, parallel group phase III trial to compare haemostatic efficacy and safety of TachoSil and argon beamer in patients undergoing liver resection.

## METHODS

### Study Participants

Hospitalised patients undergoing elective liver resection for any medical reason (mainly hepatic malignancies) were eligible for inclusion in this trial. At least segmental resection, following either anatomical demarcation lines or non-anatomical resections, had to be performed, and minor (oozing) or moderate haemorrhage persisting after primary surgical haemostatic intervention had to be present prior to randomisation of the patient to either TachoSil or argon beamer treatment.

Patients presenting with pulsating arterial haemorrhage and/or major venous bleeding did not qualify and were subjected to additional conventional haemostatic measures before becoming eligible for inclusion into this trial.

The objectives of this trial were to compare haemostatic efficacy and safety of TachoSil and argon beamer treatment in patients undergoing liver resection.

### Treatments

Primary haemostasis of major vessels was performed as usual and recorded, e.g. sutures, ligations, clips. The hepatic blood flow occlusion was unclamped and hemorrhage checked – if minor or moderate bleeding remained, patients were randomised to either TachoSil or argon beamer treatment. The number of TachoSil sponges to be applied was not prespecified in the trial protocol but depended on the patients' individual size of the bleeding wound surface, which had to be covered in total. Argon beamer treatment was applied to patients according to the routine of the surgical centre (i.e. once or twice with different duration times). The argon beamer was chosen as the comparator because it is an often used standard treatment to achieve haemostasis and tissue sealing in liver resections. TachoSil or argon beamer was applied to all resection sites. If there was more than one resection site, the largest site was measured and assessed for time to haemostasis. This was called the target site.

### Outcomes/endpoints

#### Primary endpoint:

- Time (min) to intra-operative haemostasis after application of TachoSil or argon beamer.

Counting began when the test treatment was first applied. Haemostasis was considered to have been achieved when there was no visible bleeding from the target site. Presence or absence of haemostasis was assessed at 3, 4 and 5 minutes after the first treatment had begun. If haemostasis had not been achieved by 5 minutes the treatment was repeated.

#### Secondary endpoints:

- Proportion of patients with haemostasis 10 min after initiation of test treatment without additional haemostatic measures;
- Volume of drainage fluid at day 1 and days 1+2 after surgery and haemoglobin concentration of drainage fluid at day 1 and day 1+2;
- Total post-operative duration of drainage.

### Sample size

It was planned that 140 patients should be recruited into the study in a 1:1 randomisation. However as in trial 013 recruitment was halted early, in this case when only 118 patients had been recruited (an additional 3 patients still ended up being randomised into the trial). Again the reasons given were a slower than expected recruitment rate and a calculation that there was not much power to be gained by waiting for the additional patients. It was calculated that with 140 patients the expected power was 95.3%, whereas 118 patients still gave 92.1%.

As stated for trial 013 the early termination of recruitment is problematic for an open-label study as it would be possible to monitor the results as the trial progresses and terminate recruitment after it is known that positive results have been achieved.

### Statistical methods

The ITT population was defined as the primary population. This is appropriate as the aim of the trial is to establish superiority over the comparator. The population was defined as all patients randomised and given treatment. As there were no patients who were randomised and not treated this is satisfactory. Fewer patients completed the trial in the TachoSil group. The reason for this was the greater number of deaths in the TachoSil group. If this is a real finding it would be extremely concerning.

	TachoSil	Argon
ITT population	59	62
Death	6 (10%)	2 (3%)
Other discontinuation*	0	1 (2%)
Completed the trial	53 (90%)	59 (95%)

\* travelled abroad



As in study 013 there was a difference between treatment groups in the area of the target wound, with the larger area being found in the TachoSil group. The comments made in the assessment of study 013 regarding a possible breakdown in the randomisation apply here, and are strengthened by the finding being repeated in both studies. This could create problems for the interpretation of the data. If the randomisation has not worked the trial is not comparing randomised groups and many of the assumptions underlying the statistical analyses are no longer valid.

	N	Mean (SD)	Median
TachoSil	59	84 (57)	71
Argon	63	65 (41)	57

All statistical tests were to be performed using a type I error (two-sided) of 0.05.

A log-rank test was used to compare time to haemostasis between both treatment groups. As time recordings were made only at the time points 3, 4, 5, 8, 9 and 10 minutes after start of treatment a haemostasis time less than 3 min was set to 3 min, a haemostasis time of 6 or 7 minutes was set to 8 min in the analysis. If haemostasis was obtained after 10 minutes, the observation was censored at 10 min. In addition an explorative parametric survival analysis accounting for interval censoring was performed.

The proportion of patients with haemostasis after 10 minutes treatment were compared by means of Fisher's test and, in addition by means of a Cochran Mantel Haenszel test accounting for centres.

Both treatment groups were compared with respect to volume of drainage on days 1 and 2 by means on an ANOVA. The same method of analysis was used for the comparison of treatment groups with respect to haemoglobin on both days.

A log-rank test was used to compare duration of drainage between both treatment groups.

The above-mentioned parameter as well as all other parameter was described by means of descriptive statistics.

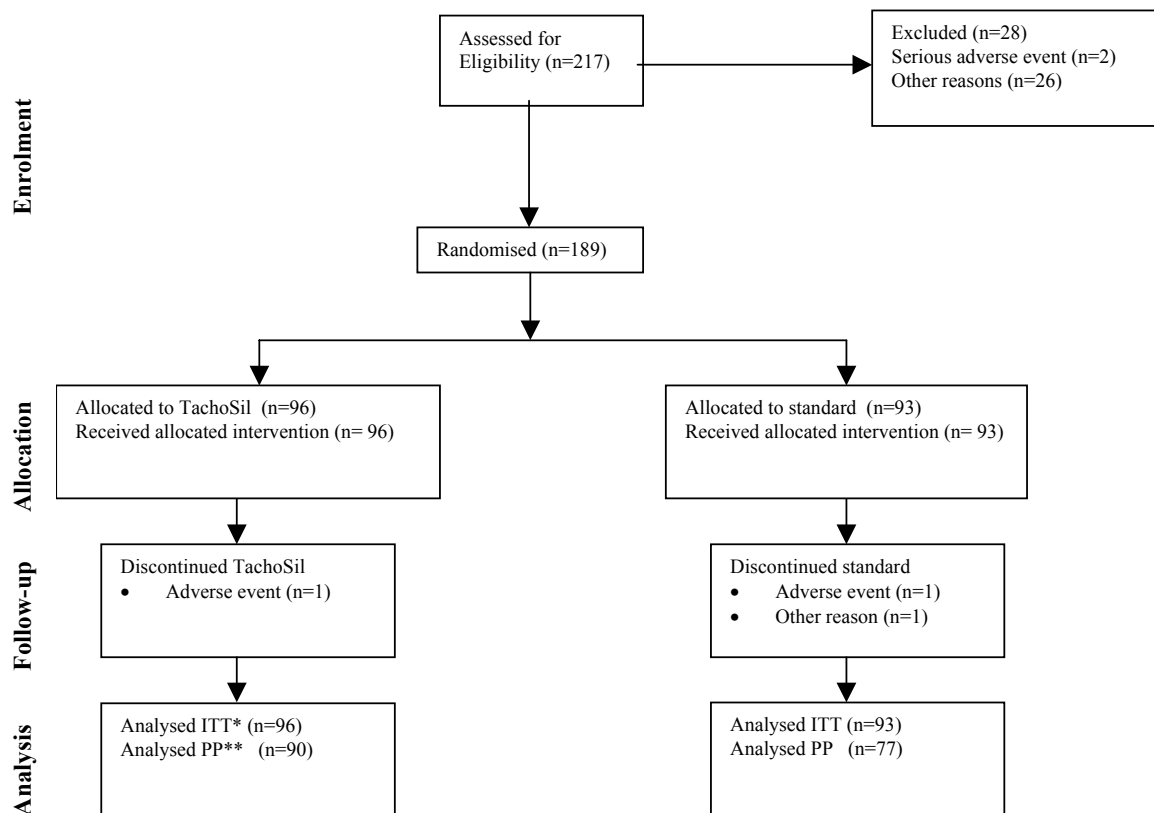
### **Study TC-016 IN**

In order to address the statistical concerns raised with study TC-014-IN, the Applicant provided the clinical study report of a second liver resection trial (TC-016-IN). Out of 149 screened patients a total of 119 patients (60 TachoSil, 59 argon beamer) at 10 centres were randomised in this open label study. Following liver resection and primary haemostasis randomisation was done by a centralised telephone randomisation system. Both treatment groups were balanced with respect to baseline demographic and general anamnestic data. With respect to the surgical data a slight imbalance in favour of the TachoSil group was to be found with respect to the number of segments resected (median: TachoSil – 2, argon beamer – 3) and the area of the target wound (median: TachoSil – 47.1 cm<sup>2</sup>, argon beamer – 63.4 cm<sup>2</sup>).

## RESULTS

### Study TC-013-N

#### Participant flow



#### Outcomes and estimation

Parameter	TachoSil	Standard	P-VALUE
Primary parameter			
Incidence of postoperative air leakage			
• ITT	33 / 96 (33%)	34 / 93 (37%)	0.76
	Odds ratio: 0.91 (95%-CI: 0.48 – 1.72)		
• PP	31 / 90 (34%)	29 / 77 (38%)	<b>0.75</b>
	Odds ratio: 0.87 (95%-CI: 0.44 – 1.72)		
Secondary parameter			
AUC of postoperative air leakage (mean)	0.77	1.27	<b>0.3</b>
Duration of postoperative air leakage (median)	1.7 days	2.0 days	0.07
Duration of postoperative chest tube drainage	4.5 days	4.6 days	0.98

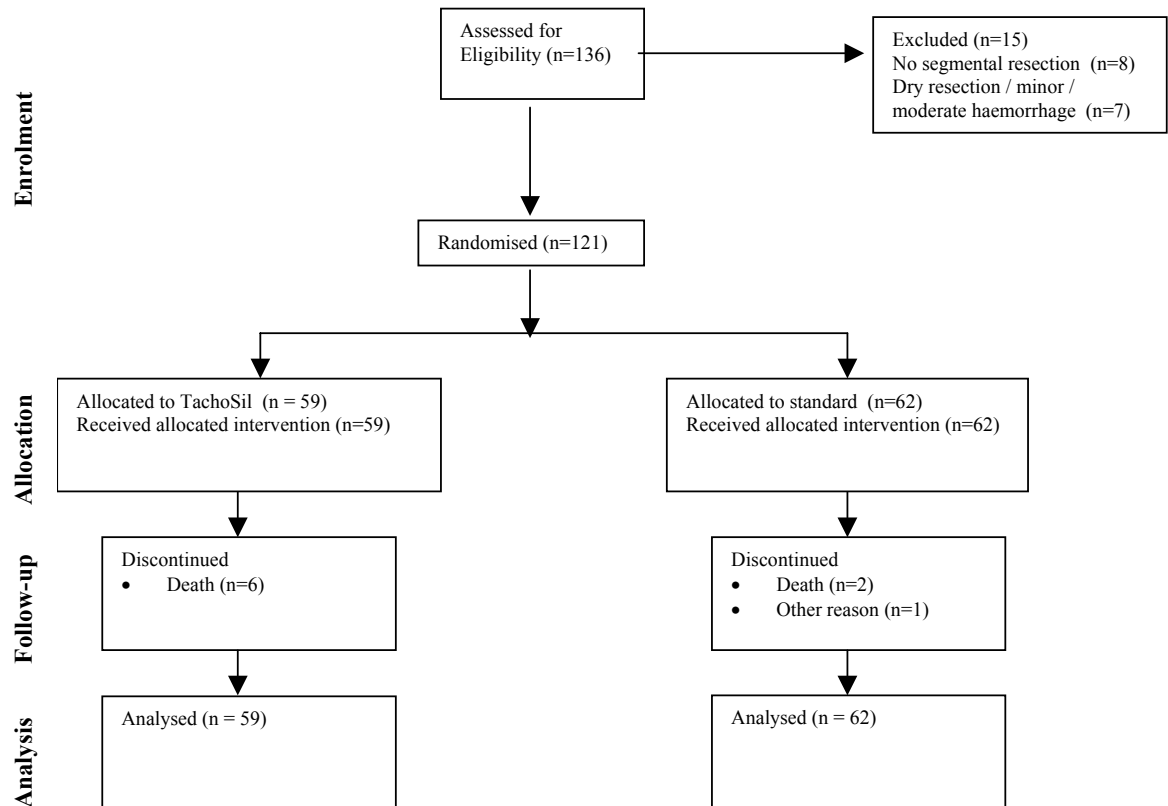
No significant findings were discovered in the analysis of the primary endpoint.

Analyses of secondary parameters such as intra- and post-operative air leakage intensity and volume of post-operative chest tube drainage overall did not reveal statistically relevant differences between the treatment groups. The results showed positive trends and did reach significance in the sub-group analysis of the grade 1-2 strata.

The advantages seen in secondary parameters in the subgroup of patients with baseline air leakage grade 1-2 have to be interpreted with caution as the primary analysis does not reveal a significant advantage for TachoSil (thus any conclusion based on secondary analyses are questionable *per se*).

### Study TC-014-IN

#### Participant flow



## Outcomes and estimation

PARAMETER	TachoSil (n = 59)	Argon beamer (n = 62)	P-VALUE
Primary parameter			
Time to haemostasis (min) (median)	<b>3.0</b>	<b>4.0</b>	0.0007*
Secondary parameter			
Proportion of patients with haemostasis after (beyond) 10 min	<b>2/59 (3%)</b>	<b>6/62 (6%)</b>	0.27
Volume of drainage fluid (ml, mean)			
• day 1	525	496	0.32
• day 1+2	865	730	0.18
Haemoglobin concentration of drainage fluid (mmol/L, mean)			
• day 1	2.0	2.2	0.32
• day 2	1.1	2.3	0.01
Duration of drainage (days)			
• mean	8.2	5.7	0.005
• median	6.0	5.1	

\* - LOG-RANK TEST

The primary efficacy endpoint was the time to haemostasis in minutes. The primary analysis was to be performed using the log-rank test. The primary analysis provides strong evidence that the time to haemostasis is reduced by the use of TachoSil as opposed to Argon, and hence that TachoSil improves the control of bleeding (subject to the methodological problems identified).

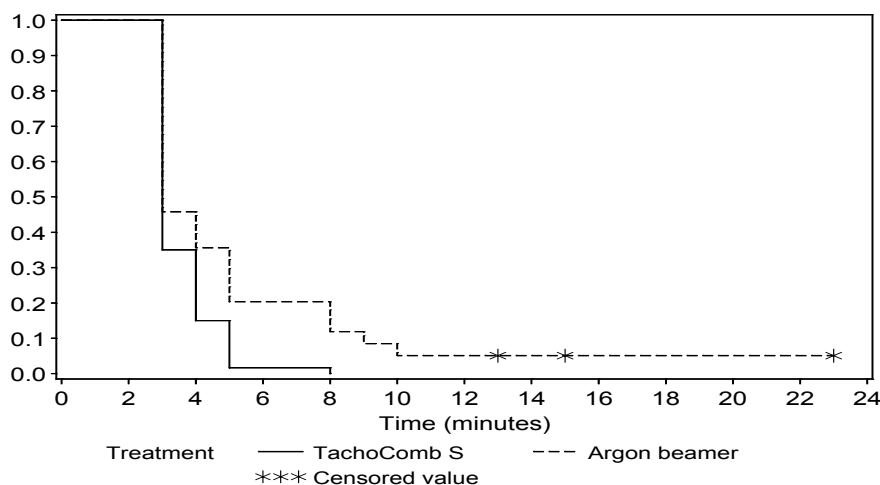
The secondary endpoints produced slightly contradictory findings. A positive finding is that the haemoglobin content of the drainage fluid is significantly lower for TachoSil, however a negative finding is that the duration of drainage is significantly longer.

### Study TC-016-IN

With regard to the primary endpoint of efficacy, time to haemostasis, the results are summarised below:

Time to haemostasis (min), ITT	TachoSil N=60	Argon beamer N=59
Mean (SD)	3.6 (0.9)	5.0 (3.6)
Median	3.0	3.0
Range	3-8	3-23

Life tables' estimates for time to haemostasis, depicting the fraction of subjects still bleeding at a given time, are shown in the figure below. The log-rank test for difference between treatment in time to haemostasis was statistical significant in favour of TachoComb S compared to argon beamer (p=0.0018, ITT population):



None of the secondary endpoints gave significant results. Total median drain volume was lower (0.6 vs. 1.1 litres) in the TachoSil compared to the argon beamer treatment group. Median duration of drainage was comparable (5 days) in both groups. Haemoglobin as well as bilirubin concentrations of drainage fluid did not differ significantly between treatment groups.

### Clinical studies in special populations

No studies in special populations were undertaken.

### Supportive studies

The Applicant provided 5 additional supportive studies with TachoComb H and TachoComb respectively.

#### Liver Resection (PHTC 009):

Study PHTC 009 was conducted in 279 patients in liver resection surgery with the aim of evaluating the efficacy and safety of TachoComb H (n=86) versus argon beamer (n=97) and no immediate secondary treatment (n=96). The patient population was virtually identical to the one in pivotal study TC-014-IN. However the study design was different from the pivotal study, as it consisted of three groups and the primary endpoint was efficacy rating by the surgeon, based on the need for additional surgical measures to obtain haemostasis. Secondary variables were blood loss, operation time and overall rating of usefulness.

The treatment was found to be effective in 91% of patients in the TachoComb H group, in 79% of the argon beamer and in 49% of the observation group. The blood loss could not be calculated, no significant differences were seen between groups in the operation time. The treatment was rated as easy to use and effective by the investigators.

#### Pulmonary Surgery (PHTC 007):

Study PHTC 007 was planned to recruit 150 patients with pulmonary air leakage, it was however terminated after inclusion of patient 92 due to concerns on centres' GCP compliance. The evaluation of the results shows TachoComb H more effective than surgical standard (p=0.0006) with efficacy scores of 8.5±2.1 and 6.2±3.5 respectively, but for the above reason the results can only be considered as additional evidence.

#### Lymphatic Sealing (TC-011-AU):

61 patients were enrolled and treated with either TachoComb H (30) or surgical standard alone (31). All patients were female undergoing axillary lymph nodes dissection due to breast cancer. One whole patch was applied along the thoracic nerve and half patch over the nerveless bundle as it enters the arm. Two different batches of product were used.

Primary efficacy was the duration of drainage, secondary efficacy included post-operative hospitalisation, time to drainage removal, drainage volume, local infection/inflammation, seroma formation.

TC-011 AU failed to demonstrate any clinical benefit of TachoComb H over standard wound management (control) as no statistical or clinical differences were found in any of the primary and secondary variables. No additional dosing information was obtained from this trial.

#### Suture hole bleeding (PHTC 006 and PHTC 008):

PHTC 008 trial was terminated after 25 patients had been enrolled, as it was unlikely to yield additional information. For this reason the data from study 008 were not subject to statistical analysis.

The results of trial PHTC 006, including 30 patients for each treatment group, was as follows:

median time to haemostasis 240 seconds (range 180-900) for TachoComb H versus 390 seconds (180-1500) in the control group. The primary endpoint was evaluated with and without co-variables (including indication, surgical centre and number of suture holes) and resulted in favour of TachoComb H in both analyses ( $p=0.0085$  and  $p=0.0034$ , respectively). The surgical centre however was a significant prognostic factor for time to haemostasis (0.0034). The incidence of local infections was lower in the TachoComb H group (3% vs. 13%). No statistically or clinically significant differences were found with respect to the other secondary endpoints between treatments.

#### **Discussion on clinical efficacy**

The Applicant has not performed any pharmacokinetic studies in humans, but refers to animal studies that have been performed with the predecessor products of TachoSil. The rationale for this approach is comprehensive. For topically used fibrin sealant and in particular for TachoSil, pharmacokinetic studies are not as important as they are for pharmaceutical products where certain blood levels of the active compound have to be achieved and sometimes also to be prevented. TachoSil will be applied topically and its efficacy can be shown by demonstrating that the clot and/or the tissue sealing is stable. This parameter, however, has been investigated in clinical studies. Concerning the metabolism of the compounds, the information gained from the animal studies, i.e. slow degradation of clot and sponge over several weeks, is considered sufficient and given the practical difficulties, do not need to be re-evaluated in humans.

No pharmacodynamic studies in humans have been performed and the Applicant refers to the animal studies undertaken. However, in these studies, pharmacodynamics was not investigated directly but via indirect parameters such as time to haemostasis. To investigate pharmacodynamics directly, the speed and the stability of clot formation and/or tissue sealing would need to be measured. There are currently no established methods to study these pharmacodynamic end-points. Thus, information on human pharmacodynamics will be gained by results of the clinical studies only.

The effect of TachoSil is based on the well-known physiological process of the final steps of the coagulation cascade and therefore the lack of specific data in man is considered to be reasonable. The Applicant has conducted animal studies to characterise TachoSil's pharmacological properties. According to this information, the fibrin clot is metabolised as the endogenous fibrin and the collagen sponge persist until its degradation (completed within ~24 weeks). It is however unclear whether the product's mechanism of action also involves physical/mechanical interaction of the solid collagen matrix with the wound surface or is only attributable to the claimed activation of the product's clotting components.

In order to demonstrate efficacy of TachoSil, the company initially submitted two pivotal studies with TachoSil, i.e. TC-013-IN, lung surgery study, and TC-014-IN, liver surgery study. Furthermore, supportive studies with the predecessor products, i.e. TachoComb and TachoComb H, have been provided. Since the predecessor products do differ in the composition of biological active compounds, these studies cannot replace studies with TachoSil.

The lung trial (TC-013-IN) failed to reach its primary objective, which was to demonstrate superiority of TachoSil over conventional surgical means. Whereas the trial on liver surgery (TC-014-IN) gave statistically significant results in favour of TachoSil with respect to the primary endpoint (time to

haemostasis) and haemoglobin concentration of drainage (secondary endpoint). The other secondary endpoints (volume and duration of drainage) showed instead an advantage for the argon beamer in liver resection. However, while showing results in favour of TachoSil with respect to the primary endpoint, the liver surgery trial (TC-014-IN) has several faults resulting ultimately in lack of internal consistency and affecting its clinical significance. Furthermore, the proportion of deaths in this study appears to be higher in the TachoSil than in the control group, therefore raising safety concerns. Additionally, no comparison has been made with any of the fibrin sealant products currently licensed in the EU.

Overall, the results in favour of TachoSil were questionable due to methodological problems of both clinical studies. The trials were performed in an open manner and either no or insufficient provisions were taken to minimise the possibility of bias or the provisions undertaken were insufficiently described. Further, both studies were prematurely terminated. The reasons provided are either not in accordance with the study protocols or the information provided is insufficient in order to comprehend the decisions leading to study termination. With reference to study TC-014-IN, it cannot be excluded that the study was terminated due to the favourable outcome at the time of termination.

Study TC-013-IN, the lung trial, showed many positive trends in favour of the active treatment but overall the study was negative. Neither a statistically significant nor a clinically relevant advantage in favour of TachoSil has been shown. One of the secondary endpoints was significant, but there was an imbalance in baseline air leakage and the positive result was not robust when a sensitivity analysis ignoring baseline was performed.

The imbalances seen in area of treatment site and baseline air leakage, with the most serious cases more likely to be entered into the TachoSil group, might indicate the possibility of the randomisation having failed, which would have serious implications for the interpretability of the data.

In the liver trial, study TC-014-IN, the primary endpoint produced highly statistically significant results in favour of TachoSil. In addition one of the secondary endpoints produced positive results. However when considering this study we must also consider certain factors which complicate the interpretation. The recruitment was stopped early, which could bias the results of an open-label trial. There was an imbalance in the area of the target wound, with the larger wounds tending to be on the TachoSil group. If there were a problem with the randomisation this would have serious implications for the interpretability of the data. Other issues are the higher proportion of deaths and the finding of longer duration of drainage in the TachoSil group.

To overcome these problems and establish the efficacy findings a new trial on liver surgery was performed by the applicant (TC-016-IN), which is methodological acceptable. Many deficiencies of previous trials have been corrected in this study, making it more robust.

With respect to the primary efficacy parameter, the results of study TC-016-IN are in line with those of study TC-014-IN. There is a statistically significant improvement in time to haemostasis for TachoSil patients when compared to argon beamer in both trials (TC-014-IN mean time to haemostasis 3.9 min vs. 6.3 min (median: 3.0 min vs. 4.0 min),  $p = 0.0007$ ; TC-016-IN mean time to haemostasis 3.6 min vs. 5.0 min (median: 3.0 min in both groups),  $p = 0.0018$ ). The effects on the secondary endpoints in study TC-016-IN are only minor and not statistically significant. The prolongation of total duration of drainage as observed in study TC-014-IN was not confirmed in study TC-016-IN (the median duration of drainage being 5 days in both treatment groups).

However, the interpretation of the positive findings on time to haemostasis in study TC-016-IN is aggravated by observed imbalances with respect to surgical data. The number of resected segments is lower in the TachoSil patients than in argon beamer treated patients (median: 2 vs. 3). The same holds for the area of target wound (47.1 cm<sup>2</sup> vs. 63.4 cm<sup>2</sup>). However, taking into account corresponding data provided by TC-014-IN, where these imbalances were the opposite way (median resected elements TachoSil/Beamer 4 vs. 3 and wound area 71 vs. 57 cm<sup>2</sup>) and the positive findings regarding the efficacy in haemostasis treatment in both studies, the efficacy conclusion is considered to be positive for TachoSil.

It is acknowledged that blinding during the surgery is nearly impossible, thus for assessment of intra-operative effects an open trial might be the only possibility. The measures to avoid bias described by

the applicant are quite vague and with respect to the observations made in study TC-013-IN and TC-014-IN it seems that these measures were not effective in all cases. Fortunately the new trial TC-016-IN has less bias problems and allows us to have more confidence in the results of study TC-014-IN.

The results from study TC-016-IN are significantly in favour of the primary endpoint 'time to haemostasis' and safety is comparable to the control procedure 'Argon Beamer', which is widely used and is a valid comparator. As the secondary end-points did not show statistically significant superiority, TachoSil cannot be accepted as superior to Argon Beamer on the basis of current information. Furthermore, the use of TachoSil for tissue sealing is not supported based on the results of the two pivotal studies mentioned above.

TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. Specific data have not been obtained on the use of this product in neurosurgery, in vascular surgery or in gastrointestinal anastomoses. The use of TachoSil is restricted to experienced surgeons.

There is currently insufficient information to recommend use in paediatric patients and this has been reflected in the SPC. The Applicant has committed to perform a prospective post-marketing study on the safety and efficacy of TachoSil in children post-marketing. Furthermore, the Applicant is currently conducting a further confirmatory clinical trial with TachoSil in renal surgery, TC-015-IN. The outcome of this clinical study will be communicated to CPMP as a post-marketing commitment.

### **Clinical safety**

Clinical safety of TachoSil was assessed in the two pivotal trials TC-013 IN and TC-014 IN and the additional study, TC-016-IN, contributing to both efficacy and safety of the product. In addition, supportive clinical safety data gathered in studies with the predecessor product, TachoComb H, which differs from TachoSil mainly by additional presence of bovine aprotinin, were presented.

### **Patient exposure**

	Patients enrolled	Patients exposed To TachoSil
Open studies	189 (TC-013-IN) 121 (TC-014-IN) 119 (TC-016-IN)	n = 96 n = 59 n = 60

The following table summarises the number of patients exposed to different dosages of TachoSil in the two pivotal trials, TC-013-IN and TC-014-IN.

Exposure to TachoSil	TC-013-IN (n=96)	TC-014IN (n=59)
1 sponge	61/96 (63.5%)	11/59 (18.6%)
2 sponges	26/96 (27.1%)	20/59 (33.9%)
3 sponges	6/96 (6.3%)	13/59 (22.0%)
4 sponges	2/96 (2.1%)	11/59 (18.6%)
5 sponges	0/96 (0.0%)	2/59 (3.4%)
6 sponges	1/96 (1.0%)	2/59 (3.4%)



Similarly, the applicants summarises the number of patients exposed to the drug in studies with TachoComb H:

TachoComb H trial	Patients exposed	Amount of sponges	Average per patient
PHTC 006	30	28.5	0.95
PHTC 007	46	65.0	1.41
PHTC 008	12	16.0	1.33
PHTC 009	89	225.0	2.5
TC-011-AU	30	45.0	1.5

The maximum dose of TachoSil or TachoComb H given to a single individual in clinical trials was six and seven sponges, respectively.

### **Adverse events**

#### TC-013-IN:

In total, 81 (43%) of the patients experienced one or more adverse events during the trial. The number of patients reporting at least one adverse event in each treatment group was: TachoSil group 39 (41%) and standard treatment group 42 (45%). The most frequent adverse event was surgical site reactions (12 and 20 events in TachoSil and standard group, respectively), fever (3 and 10 events in TachoSil and standard group, respectively), and atrial fibrillation (2 and 8 events, respectively). Only one adverse event, i.e. one case of emphysema, was considered related to TachoSil.

#### TC-014-IN:

In total, 50 (42%) of the patients experienced 97 adverse events during the trial. The numbers of patients reporting at least one adverse event in each treatment group were, TachoSil group 26 (44%) and argon beamer group 24 (39%). The most frequent adverse events were abscess (7 events), fever (7 events), post-operative wound infection (6 events), pneumonia (6 events) and gall bladder disorder (6 events). The numbers of adverse events were equally distributed between treatment groups for the total number of events as well as for causality. Four adverse events were considered possibly related to test treatment: Post-operative haemorrhage (TachoSil), anaemia (TachoSil), abscess and pleural effusion (argon beamer). Seventeen adverse events were rated as severe in the TachoSil group compared to 4 in the argon beamer group.

#### TC-016-IN:

Adverse events were reported for 25/60 (42%) of the TachoSil patients and 28/59 (48%) patients in the argon beamer group. In general, adverse events were equally distributed between treatment groups for the total number of adverse events, severity and causality. The most frequently reported adverse events were urinary tract infection, myocardial infarction, ascites, wound infection, pneumonia, pleural effusion and pulmonary failure that are well known complications to intra-abdominal surgery, e.g. liver resection. There was no significant difference in the distribution of these adverse events between the two treatment groups. Of the 92 adverse events reported, none were reported probable and four were considered possibly related to test treatment. The four possibly related adverse events were liver abscess and postoperative abscess for TachoSil and intra-abdominal haematoma and infection for argon beamer.

### **Serious adverse event/deaths/other significant events**

#### TC-013-IN:

Sixteen patients (8.5%) experienced one or more serious adverse events following randomisation, resulting in 19 events and 16 individual SAE reports. Additionally, 2 events occurred in 2 patients before randomisation. There were 13 serious adverse events in 10 TachoSil treated patients, and 6 patients in the standard group experienced a total of 6 serious adverse events. The only serious adverse event considered related to test treatment (TachoSil) was emphysema.

One patient died during screening after a haemorrhage.

TC-014-IN:

Of the 121 patients, 21 (17.5%) had a total of 37 serious adverse events, 23 events in 14 TachoSil patients and 14 events in 7 argon beamer patients. The serious adverse events were all related to the underlying medical condition or to the long-lasting and complicated surgical procedures, except for 2 events that were possible related to TachoSil (post-operative haemorrhage) and argon beamer (abscess and pleural effusion), respectively.

Eight patients died during the trial, 6 TachoSil patients and 2 argon beamer patients. The deaths were all related to complications of surgery (5 patients) or to the underlying illness (3 patients), and the uneven distribution between treatment groups seems incidental.

TC-016-IN:

Serious adverse events were to be observed in 10/60 (17%) TachoSil patients and 14/59 (24%) argon beamer subjects. No treatment specific pattern of adverse events became obvious.

Six subjects died during the trial, two TachoSil and four argon beamer subjects. No death was considered treatment related.

Supportive trials:

In all supportive trials conducted with TachoComb H, 44 serious adverse events were reported from 32 patients of the TachoComb H groups (total n=211) and 54 serious adverse events from 43 patients in the comparator groups (total n=318). None of the serious AEs were considered by the Applicant as probably or possibly related to study treatment, except for those reported in liver study PHTC 009. Six adverse events, classified as probably/possibly related, were reported in this study (two in each treatment group: TachoComb H, argon beamer, and observation). In the TachoComb H group, one female 75 y.o. Patient developed biliary fistula and underwent surgical revision. The patient recovered completely from the event. The other patient from this group, a 30 y.o. female, experienced persistent bleeding from the resection area, which required re-operation, this patient recovered completely.

**Common Adverse Events**

TC-013-IN:

The table below displays the number and type of the most frequent adverse events in the two treatment groups:

Number of patients	Total N=189	TachoSil group N=96	Standard treatment N=93
Surgical site reaction	32	12	20
Fever	13	3	10
Artrial fibrillation	10	2	8

None of the serious surgical site reactions was considered related to test treatment. One of the AEs in trial TC-013-IN is pulmonary embolism; this has been classified as non-related.

Two events in the non-serious surgical site reaction in the TachoSil group and three events in the standard treatment group were probably or possibly related but all recovered without sequelae.

TC-014-IN:

The number and distribution of the most frequent adverse events:

Adverse event	Total N=120	TachoSil group N=59	Standard treatment N=61
Abscess	8	5	3
Fever	7	3	4
Gall bladder disorder	6	4	2
Pneumonia	6	2	4
Postop. Wound infection	6	4	2

Nine of these events were classified as serious: five abscess formations (2 in patients receiving TachoSil and 3 in standard treatment) as well as three events of gall bladder disorder (2 with TachoSil and 1 standard treatment) and one case of postoperative wound infection in the TachoSil group. One case of postoperative haemorrhage was reported in the TachoSil treatment group. This was considered by the company as possibly related to TachoSil treatment (attributed by either lack of efficacy or to a bleeding vessel in the wound area covered by TachoSil). One case was fatal, all other patients mentioned above recovered without sequelae.

Supportive studies:

In the TachoComb H studies the following adverse events were recorded most frequently:

Adverse event	TachoComb H N=211	Standard treatment N=318
Fever	25 (11.8%)	30 (9.6%)
Impaired wound healing	17 (8.1%)	21 (6.7%)
Postoperative haemorrhage	12 (5.7%)	15 (4.7%)

**Laboratory findings**

TC-013-IN:

Clinically significant abnormal laboratory values developed with the same frequency in the two groups, i.e. 6 patients in the TachoComb S group and 5 patients in standard group. At screening most of the laboratory values were already abnormal (83% in TachoComb S group and 80% in standard group). On discharge over half of the subjects had improved since screening (57% in TachoComb S group and 60% in standard group).

TC-014-IN:

Clinically significant abnormal laboratory values were reported for 14 TachoSil patients and for 4 argon beamer patients. All clinically abnormal laboratory values were either already present at screening or were caused by the surgical procedures performed or by the underlying liver disease of the patient.

In all trials with TachoSil or TachoComb H, changes in laboratory parameters were recorded during study. In general, the most marked changes in haematological parameters were postoperative decreases in haemoglobin, haematocrit and erythrocyte counts, which often persisted until discharge. Coagulation parameters also changed in all trials, with: i) prothrombin time decreasing intraoperatively, ii) activated partial thromboplasting time increasing intraoperatively and at 24 hours postoperatively, and iii) thrombin time markedly increasing intraoperatively. All the changes were usually transient. According to the company, these changes reflect the intraoperative anticoagulant therapy. However, the type of anticoagulant used in the trial is not discussed.

**Thrombotic events**

*Myocardial infarctions:*

In the liver trial TC-016-IN, 3.4% of subjects developed myocardial infarction. There was no significant difference in the number of subjects developing myocardial infarction between the treatment groups with 4 subjects in the TachoSil group and 0 subjects in the argon beamer group. It should be noted that there is little statistical power of this analysis because of the small numbers, so the conclusion should be cautious. However, it is likewise statistically problematic to conclude any higher incidence of myocardial infarction in the TachoSil group compared to control patients. The higher number of events in the TachoSil thus seems incidental. All four TachoSil subjects had several risk factors for development of myocardial infarction. Two of the subjects died due to myocardial infarction and 2 subjects recovered. All myocardial infarctions were considered not related to TachoSil by the investigator.

In the lung trial TC-013-IN, no myocardial infarctions were reported. In the liver trial TC-014-IN, myocardial infarction developed in 1 subject in the TachoSil group and in none subjects in the argon beamer group. The myocardial infarction was considered not related to TachoSil by the investigator.

Furthermore, a statistical analysis (Fisher's Exact Test) based on the pooled data of all TachoSil studies shows no significant difference in the incidence of thrombotic events in general between TachoSil and the comparator (p=0.75) (see table 1).

Number of subjects with thrombotic events in TC-013-IN, TC-014-IN and TC-016-IN

<b>Adverse Event (LLT)</b>	<b>TachoSil</b>	<b>Comparator</b>
Cerebral infarction	0	1
Myocardial infarction	5	0
Pulmonary embolus	1	1
Thrombosis	0	1
Thrombosis arterial leg	0	1
Total	6	4

In conclusion, myocardial infarction is a known complication to major surgery and the incidence of myocardial infarction in liver study TC-016-IN is in line with data from the literature. The slightly higher incidence of myocardial infarction in the TachoSil group seems incidental, which is supported by data from the lung trial TC-013-IN, the liver trial TC-014-IN, and pooled data on thrombotic events from all three TachoSil studies.

*Pleural effusion:*

In liver trial TC-016-IN, pleural effusion developed in 2.5% of subjects. There was no significant difference (P= 0.24) in the number of pleural effusion between the two treatment groups with 3 pleural effusions (1 serious and 2 non-serious) in the TachoSil group and none in the argon beamer group. All three subjects had risk factors for pleural effusion. All three events were considered not related to TachoSil by the investigator.

The slightly higher number of pleural effusions in the TachoSil group seems incidental, which is supported by the findings in TC-013-IN and TC-014-IN. Pleural effusion was not reported in lung trial TC-013-IN. In liver trial TC-014-IN, pleural effusion developed in 3.3% of the subjects and was equal distributed between the two treatment groups with 2 pleural effusions (both non-serious and not related) in the TachoSil group and 2 pleural effusions (1 non-serious and not related, and 1 serious and possible related) in the argon beamer group.

*Respiratory insufficiency:*

In liver trial TC-016-IN, 3.4% of subjects developed respiratory insufficiency. There was no significant difference (P=0.62) in the number of respiratory insufficiency between the treatment groups with 3 events (all serious) in the TachoSil group and 1 event (non-serious) in the argon beamer group. The TachoSil subjects had several risk factors for development of respiratory insufficiency. None of these three events were related to TachoSil. All three subjects were treated with mechanical ventilation and recovered.

The slightly higher number of respiratory insufficiency in the TachoSil group seems incidental, which is supported by the findings in TC-013-IN and TC-014-IN. In the lung trial TC-013-IN, respiratory insufficiency developed in 0.5% of the subjects and was equal distributed between the treatment groups with 1 respiratory insufficiency in the TachoSil group and 0 in the standard treatment group. The respiratory insufficiency in the TachoSil subject was non-serious and the subject had several risk factors for respiratory insufficiency, e.g. a medical history of heart failure and malignant neoplasm of bronchus and lung, major chest operation, and general anaesthesia. The event was considered not related to TachoSil by the investigator. Respiratory insufficiency was not reported in the liver trial TC-014-IN.

**Safety in special populations**

No studies were undertaken for TachoSil in any special populations.

### **Immunological events**

Monitoring by coagulation screening tests was included in the clinical trials, however no specific immunological monitoring was performed. There is no clinical trial experience on the repeated use of TachoSil and TachoComb H.

### **Safety related to drug-drug interactions and other interactions**

No designated studies on interactions with other drugs have been performed.

### **Post marketing experience**

No post-marketing data is available for TachoSil.

The Applicant provided supportive data concerning the postmarketing experience gathered with the TachoSil predecessor products, i.e. TachoComb (containing bovine thrombin, bovine aprotinin) and TachoComb H (containing human thrombin, and bovine aprotinin). For all three products the pharmaceutical preparation, the presentation of the product and the intended clinical use are essentially identical.

TachoComb is approved in 40 countries worldwide and the first marketing authorisation was granted on 5 September 1991 in Austria. Assuming an average use of one to two coated sponges per surgical procedure per patient, the amount of sponges sold thus corresponds to a patient exposure of well over 250,000 patients, since TachoComb was first introduced.

In total, 79 adverse drug reactions have been reported for TachoComb. The relatively most frequent events reported were fever or pyrexia (body as a whole – general disorders) and post-operative wound infections, including abscess formation (resistance mechanism disorders). These adverse events, together with isolated cases of ileus, abdominal adhesion, pneumothorax, pulmonary infection, mediastinitis or cardiac tamponade, are rather common after surgical interventions and thus not considered to raise any safety concerns with respect to the product. Nevertheless, a causal relationship between fever and eosinophilia as signs of hypersensitivity and the use of TachoComb could not be excluded.

In TachoComb H, the second predecessor product of TachoSil, one of the active components of TachoComb, bovine thrombin, was replaced by a biologically equivalent amount of human thrombin. Following marketing authorisation on 12 February 2001, the product was launched in Germany. During the following period with an estimated minimum exposure of 30,000 patients, there were no reports of adverse drug reaction associated with TachoComb H.

### **Discussion on clinical safety**

The safety data submitted in support of TachoSil generally reflect the type of post-operative complications related to the surgical settings in which the trials were conducted. The data obtained from the pivotal clinical trials with TachoSil raised concerns for the safety profile of TachoSil, which to a large extent have been addressed and clarified by the Applicant, for instance by the undertaking of study TC-016-IN. Data obtained from the clinical trials with TachoSil are in line with corresponding literature and there does not seem to be a significant pattern of organ involvement for adverse events.

Based on data from the two pivotal TachoSil studies, in total three adverse events were considered related to the treatment with TachoSil. However, all three adverse events, i.e. emphysema after lung surgery, post-operative haemorrhage and one case of anaemia after liver resection surgery, are more probably consequences of the surgical procedures rather than effects of application of TachoSil. Consequently, the observed AE's do not have any consequences for the SPC.

Data from studies and postmarketing experience with TachoComb/TachoComb H also did not reveal safety concerns. However, this information is considered to be at most supportive as the predecessors do have a different composition compared to TachoSil.

Study TC-IN-014 raised major concerns since more deaths occurred among the TachoSil treated patients. From the data presented one might get the impression of bias in the patient population in the sense that TachoSil patients might have been at a higher risk of complications.

Despite of recent advances in liver surgery, morbidity and mortality rates after major liver resection are still significant. In the literature, mortality rates between 1.2% and 13.4% have been reported in different liver resection studies. In the liver resection study, TC-014-IN, an overall mortality rate of 6.6% was observed, which is within the range of mortality rates reported in the literature. There was no statistically significant difference in the number of deaths between the two treatment groups with six deaths in the TachoSil group and two deaths in the argon beamer group. However, the study was not powered to pick up differences of such magnitude. None of the deaths were considered by either the Investigator or the Sponsor to be related to the trial product. The unequal distribution of deaths between treatment groups seems incidental, which is supported by the equal distribution of deaths in the recently completed liver resection trial, TC-016-IN. While the deaths were higher in TachoSil group in the previous liver surgery trial (6/59 vs. 2/62 on argon beamer), it was lower in the new trial TC-016-IN (2/60 vs 4/59 on argon beamer).

In the liver trial TC-014-IN, a total of 37 serious adverse events (SAEs) were reported in 21 patients: 23 SAEs in 14 TachoSil patients and 14 SAEs in 7 argon beamer patients. There was no significant difference on the number of SAEs in the two treatment groups. The most frequently reported SAEs were abscess, fever, post-operative wound infection, pneumonia, and gall bladder disorder, and they were equally distributed between the two treatment groups. Of the 37 SAEs reported in the two treatment groups, only one SAE (post-operative haemorrhage) in the TachoSil group and 2 SAEs (abscess and pleural effusion) in the argon beamer group were considered by both Investigator and the Applicant to be possibly related to trial product.

Of the 92 adverse events reported in study TC-016-IN, none were reported probable and four were considered possibly related to test treatment. The four possibly related adverse events were liver abscess and postoperative abscess for TachoSil and intra-abdominal haematoma and infection for argon beamer.

The data obtained from these two clinical trials with TachoSil are in line with corresponding literature and there does not seem to be a significant pattern of organ involvement. In any case, because of methodological flaws safety assessment in TC-14-IN is difficult and causality assessments by investigators could be biased, as this was an open-label study. The composition of TachoSil, i.e. human fibrinogen and thrombin coated on equine collagen, does not raise concerns that extensive resorption of the compounds will take place, which could result in undesired systemical side effects. Topical application would not normally be expected to have extensive systemic exposure. However, for all of the six deaths in the TachoSil arm, a contribution from the test agent cannot be confidently excluded. Whether some or all of these deaths had an element of thrombotic complication is difficult to evaluate at present.

Furthermore, in study TC-016-IN, there was a definite increase in myocardial infarctions (4 vs 0) and pulmonary events such as pleural effusion and respiratory insufficiency in the TachoSil group as compared to the controls. However, this difference was not statistically significant and might be incidental.

The combined incidence in the liver trial TC-016-IN of cardio-respiratory complications, including MI, pleural effusion and respiratory insufficiency was 10 for TachoSil group and 1 for argon Beamer. This is significant from a clinical perspective because of the potentially serious consequences of cardio-respiratory complications in post-operative period. Pulmonary embolus is known to cause respiratory insufficiency and/or pleural effusion and it is generally recognised that clinical diagnosis is unreliable. The mechanism of action of TachoSil, which is primarily one of inducing thrombus formation, could be mechanistically related to the above complications. However, it is considered that it would not be appropriate to add a warning to the TachoSil SPC regarding a potentially increased risk of thromboembolic events since the data currently available are difficult to interpret and no causality link has been established. As recommended by CPMP guidance, the Applicant will monitor thrombotic events and antibodies as part of continued safety surveillance. It is considered appropriate to further investigate possible increased risk of thrombotic events through the usual pharmacovigilance tools and a post-marketing safety monitoring study. In line with the core SPC for fibrin sealants, Sections 4.4 and 4.8 of the SPC warn about thromboembolic complications if the preparation is unintentionally applied intravascularly.

There is also some concern regarding a potential interaction with concomitantly used anticoagulants such as heparin. However, from theoretical considerations an interaction with heparin is not considered likely. It is not considered appropriate to add a warning to the TachoSil SPC regarding an interaction with concomitantly used anticoagulants, as there was no evidence for this at present. This question will be further investigated as part of the post-marketing safety monitoring study.

The theoretical risks of hypersensitivity and/or allergic reactions are considered sufficiently addressed in the SPC and will also be studied as part of the safety monitoring study.

Lack of data in children is mentioned in the SPC and the Applicant has committed to perform a prospective post-marketing study on the safety and efficacy of TachoSil in children.

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

In summary the quality of the product is considered satisfactory on the basis of the submitted data. The manufacture of TachoSil as well as the manufacture of the drug substances human fibrinogen and human thrombin appears to yield consistent drug substances as well as drug product.

### **Non-clinical pharmacology and toxicology**

The Applicant provided several studies showing TachoSil to be effective in haemostasis and tissue sealing in different animal models. Investigations concerning secondary and safety pharmacology have not been performed with TachoSil, but the Applicant refers to studies performed with the predecessor TachoComb, which is considered acceptable in view of the product characteristics and the intended use.

Pharmacokinetic studies with the predecessors TachoComb and TachoComb H, have shown that after local application a slow degradation (absorption) and replacement process take place over weeks.

Degradation and replacement occur via two mechanisms: the fibrin clot is degraded partly by fibrinolysis and partly by cellular phagocytosis, while the collagen patch is degraded layer by layer by absorptive granulation tissue and converted into a pseudo-capsule consisting of endogenous connective tissue ("scar"-formation).

No single dose toxicity studies have been performed with TachoSil, but again studies have been performed with the predecessor products. Five acute toxicity studies were conducted in rats and dogs with TachoComb H, TachoComb and Tachotop. The presented data indicate a good safety profile of TachoComb preparations in rats and dogs, even after i.p. administration of doses 100-200 fold of those indicated for humans. No repeat dose toxicity studies have been performed with TachoSil. One 4-week study has been performed with TachoComb. Essentially no adverse effects were seen at doses up to 50 mg/kg.

No studies regarding the effect on reproduction and carcinogenicity have been performed with TachoSil. Again, such studies are not considered relevant in view of the composition of TachoSil and the intended use. Further, toxicological investigations, i.e. local tolerance, antigenicity and studies on impurities, did not reveal any concern in view of the safety of TachoSil. Furthermore, the risk of possible antigenicity of TachoSil is considered low in view of the composition of TachoSil, the fact that TachoSil is not intended for regular repeated administration and the information as provided.

In conclusion, the evaluation of the pharmacological and toxicological data reveals no concerns in view of the safety profile of TachoSil.

### **Efficacy**

The Applicant has not performed any pharmacokinetic or pharmacodynamic studies in humans, but refers to animal studies performed with the predecessor products. The rationale for this approach is comprehensive given the product characteristics. The mechanism of action is based on the well-known physiological process of the final steps of the coagulation cascade. The pharmacodynamics of

TachoSil was not investigated directly in animal studies but via indirect parameters such as time to haemostasis. It is considered that information on human pharmacodynamics can be gained by results of the clinical studies only.

Concerning the metabolism of compounds, the information gained from the animal studies, i.e. slow degradation of clot and sponge over several weeks, is considered sufficient and given the practical difficulties, may not need to be re-evaluated in humans.

The Applicant initially submitted two pivotal clinical trials in support of TachoSil's efficacy and safety: one conducted in pulmonary surgery and the one in liver surgery. However, the lung trial (TC-013-IN) failed to reach its primary objective. The trial on liver surgery (TC-014-IN) while showing results in favour of TachoSil with respect to the primary endpoint has several faults resulting ultimately in lack of internal consistency and affecting its clinical significance. Furthermore, the proportion of deaths in this study appears to be higher in the TachoSil than in the control group, therefore raising safety concerns.

To overcome these safety and methodological concerns and emphasising the efficacy findings a new trial on liver surgery was performed by the Applicant (TC-016-IN). Results are significantly in favour of the primary endpoint 'time to haemostasis' and safety is comparable to the control procedure 'Argon Beamer', which is widely used and is a valid comparator. As the secondary end-points did not show statistically significant superiority, TachoSil cannot be accepted as superior to Argon Beamer on the basis of current information. This study is considered methodologically acceptable.

There is currently insufficient information to recommend use in paediatric patients and this has been reflected in the SPC. The Applicant has committed to perform a prospective post-marketing study on the safety and efficacy of TachoSil in children post-marketing. Furthermore, the Applicant is currently conducting a further confirmatory clinical trial with TachoSil in renal surgery, TC-015-IN. The outcome of this clinical study will be communicated to CPMP as a post-marketing commitment.

TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. Specific data have not been obtained on the use of this product in neurosurgery, in vascular surgery or in gastrointestinal anastomoses. Furthermore, the use of TachoSil for tissue sealing is not supported based on the clinical studies performed.

The use of TachoSil is restricted to experienced surgeons.

## **Safety**

Data obtained from the clinical trials with TachoSil are in line with corresponding literature and there does not seem to be a significant pattern of organ involvement for adverse events. Data from studies and postmarketing experience with TachoComb/ TachoComb H also did not reveal safety concerns. However, this information is considered to be of minor importance as the predecessors do have a different composition compared to TachoSil.

Nevertheless there are still some concerns about the potential for thromboembolic events, which cannot be totally excluded at present time due to the nature of the available data.

The Applicant will therefore undertake a prospective, safety monitoring study as a post-marketing commitment with particular focus on thromboembolic events, immunological reactions and potential interactions. The theoretical risks of hypersensitivity and/or allergic reactions are considered sufficiently addressed in the SPC. The lack of data in children is mentioned in the SPC and the Applicant will perform a prospective post-marketing study on safety and efficacy in children.

## **Benefit/risk assessment**

Following the review of the submitted documentation, the written responses provided and the final SPC and letter of undertaking, the CPMP agreed that TachoSil has shown efficacy as supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient, that may be clinically relevant and that allows a conclusion on an acceptable benefit/risk. TachoSil has demonstrated a comparable benefit/risk in comparison with an established treatment in the clinical



studies in accordance with the requirements of the CPMP NfG on fibrin sealant products (CPMP/BPWG/1089/00).

In order to collect additional data, the Applicant has committed to undertake a prospective, safety monitoring study post-marketing, with particular focus on thromboembolic events, immunological reactions and potential interactions. Furthermore, a prospective comparative trial will be undertaken post-marketing to assess the haemostatic efficacy and safety of TachoSil in children. The Applicant will also report the results of a currently ongoing prospective, randomised, controlled trial in patients undergoing renal surgery in accordance with agreed timeframes for review by the Committee.

### **Recommendation**

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of TachoSil in the supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient (see 5.1 Pharmacodynamic properties) was favourable and therefore recommended the granting of the marketing authorisation.