Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Human Fibrinogen/Human Thrombin Sponge

Proprietary Product Name: TachoSil

Sponsor: Nycomed Pty Ltd

August 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	New fixed combination
Decision:	Approved
Date of Decision:	27 February 2012
Active ingredient(s):	Human Fibrinogen/Human Thrombin
Product Name(s):	TachoSil
Sponsor's Name and Address:	Nycomed Pty Ltd 2 Lyon Park Road North Ryde NSW 2113
Dose form(s):	Sponge, medicated
Strength(s):	5.5 mg/cm2 (human fibrinogen) / 2.0 IU/cm2 (human thrombin)
Container(s):	Blister Pack
Pack size(s):	1 sponge of 9.5cm x 4.8cm 2 sponges of 4.8cm x 4.8cm 1 sponge of 3.0cm x 2.5cm 5 sponges of 3.0cm x 2.5cm
Approved Therapeutic use:	TachoSil is indicated as an adjunct to haemostasis during surgery when control of bleeding by standard surgical techniques is ineffective or impractical.
Route(s) of administration:	Topical
Dosage:	Individualised. The sponge may be cut to the desired size
ARTG Number (s)	176631

Product background

TachoSil is a plasma-derived haemostatic agent (a biological medicine) consisting of a fixed combination of two active substances, human thrombin and human fibrinogen, coated on to a collagen sponge. It is described as a biodegradable, highly flexible, hygroscopic surgical sponge consisting of a deformable sponge, coated on the active yellow side with the active ingredients. The thrombin and fibrinogen exists as a dry coating which, upon contact with physiological fluids such as blood, lymph or physiological saline, partially dissolve and partially diffuse in to the wound surface. When the sponge is moistened, the fibrinogen is transformed to fibrin by the enzymatic action of

thrombin. The fibrin monomers spontaneously polymerises into a fibrin clot that adheres the collagen sponge to the wound surface and achieves local haemostasis.

It is to be available in three presentations, which differ in the size of the sponge but not in composition of the sponge and the coating. Each square centimetre of the active coating contains 5.5 mg of human fibrinogen and 2.0 IU of human thrombin.

The individual doses used by treating surgeons is typically from 1 to 2 sponges but the use of up to 7 sponges was reported in the clinical trials.

This AusPAR describes the application by Nycomed Pty Ltd to register TachoSil with the proposed indication

"as an adjunct to haemostasis and tissue sealing in surgery".

Related products registered in Australia are Tisseel (ARTG R 147141) and Artiss (ARTG R 163515), which are presented as frozen solutions of the two components. If registration is successful, TachoSil would be the first Fibrin Sealant Sponge registered in Australia.

The TGA has adopted the European Union (EU) *Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products* which is relevant to this application[1].

Two predecessor products of TachoSil have been previously developed: TachoComb® and TachoComb® H. All three products consist of an equine collagen sponge coated with components of fibrin sealant. The content of components per area unit of the sponge is similar in all 3 products.

Regulatory status

To date, TachoSil has been approved in 47 countries worldwide including the European Union (EU) (8 June 2004), USA (5 April 2010) and Switzerland (27 September 2004). The EU and US approved indications are outlined in Table 1 below.

Table 1. TachoSil. International Regulatory History in the EU and USA.

Country	Approval Date	Indication
TachoSil		
Austria	8 June 2004	EU: TachoSil is indicated in adults for supportive treatment in surgery for improvement of haemostasis to promote tissue sealing, and for suture support in vascular surgery where standard treatments are insufficient.
United States	5 April 2010	TachoSil is indicated as an adjunct to haemostasis for use in cardiovascular surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

The related products, TachoComb and TachoComb H were first marketed in Austria and Germany in 1991/1992 and 2001 – 2005, respectively.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

[1] CPMP/BPWG/ 1089/00 http://www.tga.gov.au/pdf/euguide/bpwg108900en.pdf

II. Quality findings

Initial advice from TGA's Office of Devices Authorisation (ODA) indicated that this product should be considered a Medical Device with a medicine component and would be considered a Class 3 device under Schedule 2, Part 5.1 of the Therapeutic Goods (Medical Device) Regulations 2002. However, under subsection 41 BD(3) of the Act a declaration was made on articles that are not Medical Devices (GN23, 16 June 2010, pg 1214). This Order states:

> *3. For the purposes of subsection 41BD(3) of the Act, the following articles, or classes of articles, are declared not to be medical devices:*
>
> *(d) articles incorporating tissues, cells or substances of human origin, other than medical devices incorporating stable derivatives of either human blood or human plasma that act on, or are likely to act on, the human body in a way that is ancillary to the device;*

Based on this definition it has been decided that thrombin and fibrinogen are not 'stable derivatives of blood' (the Regulations do not define 'stable derivative of human blood or human plasma') and therefore is to be regulated as a medicine and not a medical device.

As per the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), the active substances fibrinogen and thrombin have been exempted from the Scheduling Standard (Appendix A General Exemptions: Human blood products including...(c)(v) fibrinogen and (viii) thrombin).

Drug substance (active ingredient)

Human thrombin

Structure

Thrombin is a glycoprotein with a molecular weight of approximately 39,000 Dalton (D). It is formed by two peptide chains of 36 and 259 amino acids respectively, linked by disulfide bonds. Three important sites have been identified on the surface of the enzyme: The catalytic site that confers to the molecule its serine protease activity, the exosite I responsible for the binding of the substrate (fibrinogen or thrombin receptor) and the exosite II responsible for the binding of antithrombin III and inactivation of thrombin. The structure of this protein is well established within the published literature.

Manufacture

The source and safety of the plasma has been satisfactorily addressed in the associated plasma mater file (PMF).

Physical and chemical properties

The serine protease Thrombin is a coagulation protein that has many effects in the coagulation cascade. It is the final proteolytic enzyme of the coagulation process and converts soluble fibrinogen into insoluble strands of fibrin, as well as catalysing a number of other coagulation-related reactions. Thrombin is not a normal constituent of the circulating blood but it is generated from the catalytic cleavage of its plasma precursor, prothrombin by the activated Stuart factor (Factor Xa).

The earliest identified function of thrombin is the cleavage of fibrinogen into fibrin monomers and the activation of the fibrin-stabilizing factor (Factor XIII) and protein C. Thrombin generates fibrin monomers by cleaving fibrinopeptides A (FPA) and B (FPB) from fibrinogen. Fibrin monomers spontaneously polymerise to form a soluble fibrin clot,

which is then rendered insoluble by the action of Factor XIII. Human Thrombin is a purified concentrate of thrombin derived from human plasma.

Specifications

Human Thrombin Active Substance is present in the starting material, human plasma from which it is purified.

Appropriate validation data were submitted in support of the test procedures.

Stability

A shelf life of 60 months at +2 to +8 °C for Human Thrombin Active Substance is claimed based on a stability study conducted with three full-scale batches of lyophilized final product Stability data have been generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. The real time data submitted support a shelf life of 60 months when stored at +2 to +8 °C.

Human fibrinogen

Structure

Fibrinogen is a soluble plasma glycoprotein with a molecular weight of approximately 340 kD and circulates in plasma as a precursor of fibrin. The native molecule is a homo-dimer, in which both subunits consist of three different polypeptide chains (Aα, Bβ and γ). All three polypeptide chains of the subunits, as well as the dimer, are linked with disulfide bonds. The genes coding for the three different polypeptide chains of fibrinogen are located on the long arm of chromosome 4.

The three pairs of polypeptide chains named (Aα, Bβ and γ) are composed of 610, 461, and 411 amino acids, respectively. Each arm of the fibrinogen contains single Aα, Bβ and γ chains from each of the three pairs of polypeptide chains. The central domain is a dimeric structure in which both subunits contain the three amino terminals of the individual arms. The slightly thickened amino terminal ends of the Aα and Bβ chains represent fibrinopeptides A (FPA) and B (FPB), respectively, which are not present in fibrin. The dimeric halves of the central domain are held together by three of eleven disulfide bonds, the rest of which are located between the Aα and Bβ and in the junctions between the central domain and the coiled-helices. These coiled-helices are composed of the single Aα, Bβ and γ chains supercoiled as α-helices. Six disulfide bonds in each coiled-helix are responsible for the supercoil structure and for the attachment to the central and lateral domains in the form of disulfide rings.

Manufacture

The source and safety of the plasma has been satisfactorily addressed in the associated PMF.

Fibrinogen is a physiological substrate of three enzymes: thrombin, Factor XIII and plasmin. Thrombin cleaves the Aα and Bβ chains releasing FPA and FPB from the central domain. FPA is separated rapidly. The remaining molecule is a soluble fibrin monomer. The far slower removal of FPB results in formation of fibrin II that is capable of polymerisation. The polymerisation occurs by first end-to- end and then side-to-side aggregation of fibrin monomers. The resulting fibrin (urea soluble) is stabilised in presence of calcium ions, by the activated Factor XIII, which acts as a transglutaminase. Factor XIIIa-induced cross-linking of fibrin polymers renders the fibrin clot more elastic and more resistant to fibrinolysis. Cross-linked fibrin is the result of the coagulation cascade and provides tensile strength to a primary hemostatic platelet plug and structure to the vessel wall as normal repair processes take place.

Human Fibrinogen is a purified concentrate of fibrinogen derived from human plasma. Following reconstitution, the solution is almost colourless and clear to slightly opalescent. The structure of this protein is well established within the published literature.

Specifications

Human Thrombin Active Substance is present in the starting material, human plasma from which it is purified.

Appropriate validation data were submitted in support of the test procedures.

Stability

A shelf life of 60 months at +5 °C (± 3°C) for Fibrinogen Active Substance is claimed based on three stability studies.

Overall, a 60-month shelf-life at +5oC is supported.

Drug product

Formulation(s)

TachoSil consists of an equine collagen sheet coated on one side with the active substances human fibrinogen and human thrombin. The coating also contains the excipient Riboflavin to mark the active surface.

TachoSil is produced in three sizes (thickness □ 0.5 cm) with the following dimensions (length x width):

Standard size: 9.5 cm x 4.8 cm = 45.6 cm^2

Midi size: 4.8 cm x 4.8 cm = 23.0 cm^2

Mini size: 3.0 cm x 2.5 cm = 7.5 cm^2

Specifications

Appropriate validation data were submitted in support of the test procedures.

Stability

The ongoing stability study conducted demonstrated that TachoSil is stable for up to 12 months. In agreement with the TGA adopted EU stability testing guideline[2], a 12 month at the intended storage conditions (of the proposed 36 months study) has been provided. Therefore, a shelf life of 3 years can be recommended for TachoSil when stored ≤25 °C.

Also as per the TGA adopted EU guideline[2], Nycomed has committed to completing the 36-month stability study for the fourteen TachoSil Bulk batches to firmly establish the shelf life.

The sponsor is required to notify the TGA of any Out-Of-Specification (OOS) result that arise from the study.

Biopharmaceutics

Biopharmaceutic data are not required for this product because the application was not submitted as a biosimilar product with any other currently in the ARTG.

[2] CPMP/ICH/2736/99. Q1A (R2) Stability Testing of New Substances and Products (revised November 2003) http://www.tga.gov.au/pdf/euguide/ich273699r2en.pdf

Quality summary and conclusions

The quality data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Issues of concern

The Sterility Safety evaluation raised questions which need to be satisfactorily resolved. Specifically;

i. The sponsor was asked to clarify manufacturing process details.

ii. Clarification/comment was also sought from the company on the validation of the bioburden method.

These issues were addressed by the sponsor in a letter dated 19 December 2011.

Recommended conditions of registration

Batch release testing

When all the outstanding issues are resolved, specific conditions of registration were recommended to the Delegate (these were supported by the Delegate; see *Outcome* below).

III. Nonclinical findings

Introduction

In clinical practice, if 2 sheets are used, the dose administered would be approximately 20 mg/kg for a 50 -kg person (TachoSil weighs approximately 500 mg). Under "Dosage and Administration", the Product Information document states that "in clinical trials, the individual dosages have typically ranged from 1 to 2 patches" (45.6 cm^2), and that "application of up to 7 patches has been reported". If 7 sheets are used, the dose administered would be approximately 70 mg/kg.

The products used as TachoSil substitutes in several of the nonclinical studies submitted, that is TachoComb (a precursor of TachoSil with bovine thrombin and aprotinin) and TachoComb H (a precursor of TachoSil with bovine aprotinin and human thrombin), are relevant to the current product because the differences in the components are not substantial from a toxicological viewpoint. Adequate comparability studies were conducted, comparing the pharmacodynamic properties of TachoSil directly with its predecessors. A direct toxicological comparison of TachoSil with its predecessors TachoComb and TachoComb H was not conducted but due to the patches' essential similarities this was not considered necessary.

Nonclinical studies focussed on local tissue responses in different species after a single intraperitoneal application of TachoSil, TachoComb or TachoComb H to intact or wounded organs (such as liver or spleen). A conventional nonclinical submission with products such as TachoSil is not generally considered necessary because species-specific immune responses to human proteins would confound findings. However, the nonclinical data package for this application adequately addressed product efficacy, comparative efficacy, local tolerance (at different application sites) and systemic toxicity, after single and repeated (maximum of 4 applications, over a month) applications.

Pharmacology

Primary pharmacology

The pharmacodynamics of TachoSil was investigated both *in vitro* (adhesive strength) and in animal studies (adhesive strength and other parameters such as time to haemostasis under different conditions). The mechanism of action is based on the well known physiological process of the final steps of the coagulation cascade. TachoSil and predecessors TachoComb and TachoComb H were used for these studies.

The highest adhesive strength (to a plate) of TachoComb was found when the sponge was permeated with saline for less than 3 minutes and pressed for 3 – 5 min. The maximum adhesive strength to the wound/occlusive pressure was found with fibrinogen concentrations of 6 mg/cm^2 and 2 IU/cm^2 of bovine thrombin, *in vitro*, in a rat kidney wound, and rat liver wound. These values support the proposed clinical levels. Further increases of fibrinogen and thrombin did not lead to a further increase in the occlusive pressure.

Adhesive and occlusive strength of TachoComb was superior to various types of collagen sheets and liquid fibrin adhesive agents in rat and dog *in vivo* models and in guinea pig and rat *ex vivo* models. The adhesive strength of TachoSil was essentially the same as TachoComb and TachoComb H and higher than native fibrin gluing products and other sponges.

Although TachoSil is not proposed to be indicated in the cardiovascular system or the central nervous system, there was no difference in the activity of TachoSil and TachoComb H in the brain of rabbits even under hyperfibrinolytic conditions or between TachoSil and TachoComb in aortic stab wounds in pigs even under heparinised conditions.

The results confirmed that thrombin and fibrinogen concentrations present in TachoSil and its predecessors provide the strongest attachment of the sponge to lesions, compared with other concentrations.

No differences in efficacy were observed between TachoComb H and TachoSil in haemostasis and attachment to liver lesions in dogs, splenic lesions in pigs and dogs even under elevated intrasplenic blood pressure. No rebleeding from the application site was observed after gently pressing the sponge to the wound for 2-5 minutes, which is the intended use of TachoSil. Haemostatic and tissue sealing properties of TachoComb were preserved even under disturbances of the coagulation process (after administration of warfarin or heparin to rats).

Taken together, the results of the nonclinical studies suggest that the efficacy of TachoSil and its predecessors is not significantly different, therefore TachoSil's efficacy is not affected by the absence of aprotinin.

There were no studies in which the application of a sealant sponge was compared with no application of any sponge as a negative control. However, haemostasis was achieved with the sponges after gently pressing for up to 5 minutes (which is the intended administration instruction) even under hypocoagulability states and with higher adhesive strength than various collagen sheets and liquid fibrin adhesive agents that they were compared to. It is therefore expected that the time to haemostasis obtained with the clinical use of TachoSil would be significantly lower than that obtained without any treatment. Although no studies were conducted to compare TachoSil or its predecessors with the efficacy of sutures or other haemostatic measures, this is acceptable as TachoSil is not intended to be used as the only method of haemostasis but rather as an adjunct for haemostasis and tissue sealing during surgery.

The proposed indication therefore suggests that the efficacy of haemostasis during clinical use of TachoSil (which will probably include the use of other methods of haemostasis) is supported by nonclinical studies.

The mechanisms of action of fibrin sealants (fibrinogen/thrombin products) and their function in blood coagulation are well studied and understood.

It is noted that the ratio of collagen, fibrinogen and thrombin was different between the different products used in the studies, including differences within the same sponge. However, the content of the active constituents fitted within the proposed limits at release for TachoSil.

Overall, the primary pharmacology studies adequately demonstrated that TachoSil and its predecessors provide effective tissue sealing in situations that mimic its intended clinical use. No animal treated with TachoSil or its predecessors died due to haemorrhage (or any other reason) in the nonclinical development program. There was adequate evidence for pharmacological equivalence between TachoSil , TachoComb and TachoComb H, which contributes to the validity of using toxicity studies with TachoComb and TachoComb H to support the safety of TachoSil.

Safety pharmacology

Safety pharmacology data are based on studies performed with TachoComb (containing equine collagen, human fibrinogen, bovine thrombin and bovine aprotinin) in rats, guinea pigs and dogs.

The sponge was administered intraperitoneally (IP) at doses of up to 780 mg/kg in dogs (11-39-fold the clinical dose of 20-70 mg/kg, or 2-7 sponges in a person of 50 kg) and 672 mg/kg in rats (10-34-fold the clinical dose) and compared with sham-operated control animals and with animals receiving a microfibrillar collagen haemostat and collagen sponges (Nycomed). Fibrinogen, bovine thrombin and aprotinin were also examined in isolated organ experiments (guinea pig ileum, rat uterus). Studies performed in guinea pigs with varying concentrations of fibrinogen were also submitted.

No changes were seen in the respiratory and cardiovascular systems in the dog, or the following measured parameters in rats: general behaviour, pain sensitisation, spontaneous motor activity, sodium pentobarbital-induced sleeping time, induced convulsions, body temperature, fibrinolysis/coagulation, and gastrointestinal transit, urinary volume, electrolyte excretion and effects on coagulation and fibrinolysis. Inhibition of ileal contractions in guinea pigs and an increase in uterine motility in rats were observed at high doses of thrombin but are not expected to be a safety concern for the clinical use of TachoSil.

Pharmacokinetics

IP administration of radioactively labelled (^{125}I) fibrinogen TachComb to a hepatic wound in rats resulted in rapid (maximum value at 6 hours after application in all tissues except thyroid gland) and wide tissue distribution, with concentrations in tissues being similar to that observed in plasma (except for thyroid gland and hepatic application site). The decrease of labelled fibrinogen at the site of application suggested that TachoComb was absorbed intraperitoneally and the appearance of radioactivity within the rat liver tissue demonstrated the possible absorption of TachoSil components directly by liver tissue. Fourteen days after application the concentration in tissues had decreased to between 0-8% in most tissues and to 17% in the thyroid gland. In different experiments, the size of sponges implanted IP disappeared over time, suggesting absorption and metabolism of components of the sponge.

Since the components of TachoSil are endogenous compounds, the lack of studies of protein binding, metabolic pathways and possible interaction with the cytochrome P450 system is acceptable.

The degradation of TachoTop, TachoComb, TachoComb H and TachoSil was assessed indirectly by the histopathological examination of the implantation site to determine the size of remaining sponge components in different animal species and tissues.

TachoSil (48.5 mg/kg) implanted in the liver and spleen of minipigs was still visible after 12 weeks, TachoComb H (32 mg/kg) had not disappeared completely after 24 weeks in dogs whereas TachoComb (98.7 mg/kg) had disappeared completely after 16 weeks in rats. These pharmacokinetic studies with TachoSil and predecessors TachoComb and TachoComb H, showed that after local application slow biodegradation and replacement by granulation tissue occurred more than 24 weeks. The degradation process of human thrombin and fibrinogen are not expected to differ considerably from that of endogenous proteins in treated patients.

Excretion of radioactivity after IP application of ^{125}I-fibrinogen labelled TachoComb sponge to a hepatic wound in the rat was accomplished mostly via urine (89.3% after 21 days). At 21 days, around 3.9% of the dose had been excreted via the faeces and 0.4 and 6.4% of the dose remained in the thyroid gland and the rest of the organism, respectively.

Toxicology

More than 2 animal species were used for toxicity studies. The number of animals used was adequate and the route of administration (IP into abdominal organs) was appropriate as this is the intended route of administration. The dose levels used revealed limited toxicity of TachoSil and its predecessor, and given the relative dose achieved during the studies (25-50 times a clinical dose of 2 sponges in a 50-kg person), they are considered sufficient to suggest safety during clinical use.

Single dose toxicity studies were conducted with TachoSil, TachoComb and TachoComb H. TachoSil differs from TachoComb H only in lacking the bovine aprotinin. The results obtained with the predecessor products are thus considered relevant.

No animal treated with TachoSil or its predecessors died due to haemorrhage (or any other reason) in the nonclinical development program.

Systemic toxicity

Single dose toxicity studies were performed with TachoSil in minipigs and TachoComb H in dogs and rats.

No effects that were attributable to the administration of either sponge were observed with doses of up to 500 (dogs) or 1000 mg/kg (rats) TachoComb H, or up to 581 mg/kg TachoSil in minipigs, that is, about 7-50 times the clinical dose for humans (2-7 sponges or 20-70 mg/kg in a 50-kg person).

A lack of systemic toxicity was confirmed by the lack of in-life findings during the 2-4 weeks observation periods in these studies. Microscopically, there were no notable findings except at tissues involved in the operation.

Absorbed active components of TachoSil, fibrinogen and thrombin, might influence the coagulation of patients, however no effects in coagulation parameters were observed in the studies submitted (except for an isolated increase in thrombin time in rats receiving 100-1000 mg/kg in one study, which is 5-50 times a clinical dose of 2 sponges in a 50-kg person).

In summary, single application of between 7 and 50 times the intended clinical dose (2 standard size sponges) did not cause adverse events observable up to 4 weeks after surgery.

Repeat-dose toxicity

As the proposed indication for TachoSil is for intrasurgical use, the sponge is not expected to be used repeatedly and repeated dose toxicity studies do not seem to be relevant. Also, because TachoSil contains human fibrinogen and thrombin, the potential development of anti-human antibodies in animals upon repeated administration could confound the findings in any repeat-dose toxicity study performed. Nonetheless, one toxicity study was performed with TachoSil and one with TachoComb in which the sponges were applied more than once.

In a 4-week study TachoComb was administered to rats IP once weekly for 4 weeks. No adverse effects were seen at doses around 1.3-4.5 times the intended clinical dose (2-7 sponges/person). After administration of 10-36 times the intended clinical dose, slight effects were observed on food and water intake and in white blood cell (WBC) counts. Dose related adhesions of the sponges with the operated site or intraperitoneal organs were observed.

In the TachoSil study, a total dose of 79.1 mg/kg was applied to minipigs (divided into 2 doses on the liver or spleen on Days 1-2 and a dose in the spleen on Day 22). With this dose (1.1-3.9 times the intended clinical dose of 20-70 mg/kg) no adverse effects were observed. A third of the animals developed antibodies against equine collagen.

Genotoxicity

The standard battery of genotoxicity studies have not been conducted but this is generally not required for a biological product.

Carcinogenicity

The sponsor conducted a carcinogenicity risk assessment. In it, it was argued that standard *in vivo* carcinogenicity testing has not been carried out with TachoSil or its components due to the product components (homologous human proteins), the expected single dose administration of the product, the fact that a 2 year animal study would be inappropriate for this kind of product and the lack of evidence for carcinogenicity potential in other sealants containing thrombin and fibrinogen or collagen-based medicines and devices. These arguments are acceptable. Furthermore, the production of antibodies against the components of TachoSil in animal studies could limit the value of information obtained from a carcinogenicity study.

Reproductive toxicity

No reproductive toxicity studies have been conducted but this is not considered a deficiency for this type of product.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2. This category is appropriate and in accordance with other products containing fibrinogen and thrombin, and used for similar indications.

Local tolerance and antigenicity

Local tolerance was investigated during pharmacodynamic and pharmacokinetic studies. Topical application through laparotomy to intact and injured livers and spleens caused no discernible local toxic effects that could be attributed to the sponge.

Microscopically, signs of inflammation and granulation were observed but they were considered to be part of the healing process. The sponge was almost completely dissolved within 24 weeks *in vivo* in animal studies, therefore long term local tolerance issues are not expected. It is expected that the sponge will be used only once per patient.

In all studies, local tissue responses were consistent with tissue healing and degradation of the product. There was no evidence of re-bleeding or of local and adjacent tissue intolerance. Adhesions between the operated site and adjacent tissues were observed in some cases, however adhesions are an anticipated outcome of intra-abdominal surgery, and TachoSil or its predecessors did not appear to increase the incidence of adhesions in animals.

Application of TachoComb IP in rats (once weekly for 4 weeks) did not cause antibody reactions. In guinea pigs, although TachoComb was immunogenic, the immunogenicity was caused by human fibrinogen, rendering it not likely to be clinically relevant. Equine collagen (TachoTop) did not cause erythema when administered into skin pockets to guinea pigs. In minipigs however, one third of animals receiving TachoSil developed low antibody titers against equine collagen with none of the mini-pigs revealing any evidence of systemic effects of antibodies leading to immune reactions or impaired haemostasis.

No neoepitope formation was observed for any of the proteins present in TachoSil when they were sterilised by gamma-irradiation.

Compared to the predecessor products, TachoSil is free of bovine components as both fibrinogen and thrombin are of human origin. In addition, TachoSil does not contain bovine aprotinin. Taken together, results from local tolerance and antigenicity studies did not reveal clinically relevant safety concerns regarding IP administration of TachoSil. Furthermore, the risk of possible antigenicity of TachoSil is considered low in view of the composition of TachoSil and the fact that it is not intended for repeated administration. However, due to the possibility for the development of antibodies against equine collagen, the risks of immunogenicity will need to be assessed within the clinical evaluation.

Paediatric use

TachoSil is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The nonclinical part of this submission consisted of studies conducted with TachoSil or with precursors TachoComb H or TachoComb. In contrast to TachoSil , TachoComb and TachoComb H contain aprotinin, and TachoComb's thrombin is bovine in origin (rather than human). Although all the studies were not conducted with exactly the same product as is intended to be registered, the results of the studies are considered relevant and applicable to this application.
- Nonclinical primary pharmacodynamic data have been generated in vitro and in dog and rat models of hepatic and splenic wounds. The use of TachoSil and its precursors resulted in haemostasis from induced wounds to intraperitoneal organs and attachment of the sponge. The concentrations of thrombin (2.0 IU/cm2) and fibrinogen (5.5 mg/cm2) selected showed the highest tensile resistance. The

nonclinical data support the use of TachoSil as an adjunct for haemostasis and tissue healing.

- A number of safety pharmacology studies performed in rats, dogs and guinea pigs were submitted that provided information related to the effect of TachoComb on the nervous system, respiratory and cardiovascular systems, uterus and ileum. Inhibition of ileal contractions and increase in uterine motility were observed but only at high doses of thrombin. Findings in other organ systems were unremarkable.
- Excretion of sponge-related material was predominantly via urine in the species examined (rats). The in vivo biodegradation of TachoSil was almost complete within 16-24 weeks in nonclinical studies in dogs and rats. Degradation occurred primarily via infiltration of phagocytic cells and formation of granulation tissue.
- A conventional nonclinical data submission with products such as TachoSil is not generally required because species-specific immune responses to human proteins could confound repeat-dose findings. However, the nonclinical data package adequately addressed product efficacy, comparative efficacy and local tolerance at intraperitoneal tissue sites. There was also adequate investigation of potential systemic toxicity. No evidence for systemic toxicity was found in animal studies after intraperitoneal application of the proposed product or related products at doses 25-50 times the clinical dose of 2 sponges in a 50-kg person.
- No genotoxicity or reproductive toxicity data were provided and this is acceptable due to the nature of the components of TachoSil.
- The sponsor completed a carcinogenic risk assessment analysis to address potential long-term adverse effects from product use. The lack of carcinogenicity studies was acceptable and the carcinogenicity potential of TachoSil is not expected to be higher than that of fibrinogen/thrombin sealants available in Australia.

Nonclinical conclusions and recommendations

- Pharmacology studies support TachoSil's use as an adjunct for haemostasis and tissue sealing during surgery.
- Nonclinical studies provided adequate evidence to support the use of TachoSil for reducing bleeding time and blood loss when applied intraperitoneally to a variety of dissected peripheral tissues in animals. There was no evidence for local adverse effects or systemic toxicity when TachoSil (or a comparable formulation) was applied to intraperitoneal tissues.
- The risks of immunogenicity towards equine collagen, thromboembolic episodes and re-bleeding at target sites will need to be assessed within the clinical evaluation
- Amendments to the draft Product Information were recommended.
- There were no nonclinical objections to the registration of TachoSil for the proposed indication.

IV. Clinical findings

Introduction

A total of 11 Phase III and IV clinical trials have been conducted (see Table 2 below), of which 6 provide pivotal efficacy and safety data (TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM and TC-023-IM). In addition there was one Phase IV safety trial (TC-018-IN), an uncontrolled paediatric trial (TC-019-IN) and three other uncontrolled trials which provided additional safety data (TS-001-WE, TC-022-IT and TC-027-DE). The application also noted three ongoing studies (TC-026-JP, TC-029-IM and TC-031-DE) although minimal information on these was provided as part of this application.

No significant Good Clinical Practice (GCP) aspects were noted.

Pharmacokinetics

TachoSil is intended for topical application only. Pharmacokinetic studies were not performed in humans. Animal studies revealed that TachoSil demonstrated progressive degradation, with the fibrin clot being metabolised by fibrinolysis, and the collagen sponge being degraded by phagocytosis and ingrowth of granulation tissue. Animal studies revealed that approximately 13 weeks after application only a few remnants were present with no signs of local irritation.

Pharmacodynamics

No pharmacodynamic studies were performed on humans due to ethical issues with testing on normal humans as well as the fact that the active constituents, human fibrinogen and human thrombin are well established in clinical use.

TachoSil contains fibrinogen and thrombin as a dried coating on the surface of a collagen sponge, Upon contact with physiological fluids such as blood, lymph or physiological saline solution, the components of the coating dissolve and partly diffuse into the wound surface. Fibrinogen is converted into fibrin monomers which spontaneously polymerise into a fibrin clot that adheres the collagen sponge to the wound surface and achieves haemostasis. The fibrin is subsequently cross-linked by endogenous Factor XIII, creating a firm mechanically stable network with good adhesive properties and therefore providing sealing as well.

Efficacy

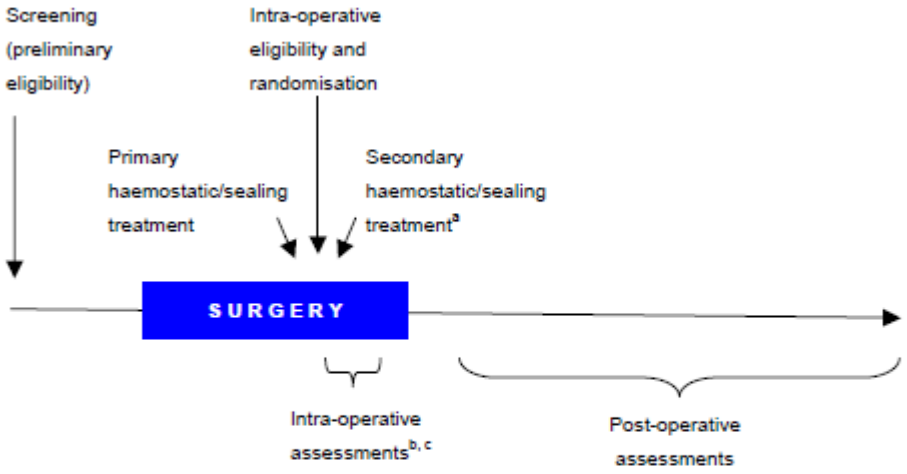
Introduction

Information on clinical efficacy was provided by 6 pivotal studies and of these, four studies (TC-014-IN, TC-015-IN, TC-016-IN and TC-023-IM) were designed to evaluate the *haemostatic efficacy* and safety of TachoSil in three different surgical applications. These were open-label, multi-centre, randomised, controlled, parallel-group studies that compared TachoSil with surgical standard treatment. Comparator treatments used in these trials were argon beam coagulator, standard surgical techniques (additional suturing) or haemostatic fleece material without additional active coagulation-stimulating compounds. The different surgical applications were liver resection (TC-014-IN and TC-016-IN), kidney resection (TC-015-IN) and cardiovascular surgery (TC-023-IM).

Two pivotal studies (TC-013-IN and TC-021-IM) were designed to evaluate efficacy in *tissue sealing* following lung lobectomy surgery. These were randomised, open, parallel-

group, multi-centre trials comparing the intra- and post-operative effect of TachoSil treatment versus standard surgical treatment as secondary treatment of air leakage in patients undergoing lung lobectomy. The general schema for all pivotal studies is included below (Figure 1).

Figure 1. General Schema of Procedures for the TachoSil Trials



[a] TachoSil or standard haemostatic/sealing (comparator) treatment.
[b] The primary endpoint in trial TC-023-IM was assessed at 3 minutes after first application of trial treatment. The primary endpoint (time to haemostasis) in trials TC-014-IN, TC-015-IN, and TC-016-IN was assessed at 3 to 10 minutes after the first application of trial treatment (i.e. the secondary haemostatic treatment).
[c] The secondary endpoint, reduction of intra-operative air leakage intensity, was measured in trials TC-013-IN and TC-021-IM.

Table 2. Summary of clinical efficacy studies. All clinical studies.

	Surgical indication	Study code	Treatments	N
1	Lung lobectomy	TC-013-IN	TC-S vs. standard surgery	189
2	Liver resection	TC-014-IN	TC-S vs. argon beamer	121
3	Kidney resection	TC-015-IN	TC-S vs. standard surgery	185
4	Liver resection	TC-016-IN	TC-S vs. argon beamer	119
5	A range of surgeries	TC-018-IN	TC-S (no comparison)	≅3170
6	Liver resection (children)	TC-019-IN	TC-S (no comparison)	16
7	Lung lobectomy	TC-021-IM	TC-S vs. standard surgery	301
8	Cardiovascular surgery	TC-023-IM	TC-S vs. haemostatic fleece	120

Dose response study

Not applicable.

Main (pivotal) studies

Study TC-013-IN

This study was an open, randomised, prospective, multicentre, parallel-group Phase III trial to compare efficacy and safety of TachoSil versus standard surgical treatment in patients undergoing **lobectomy for lung cancer** and requiring treatment for air leakage after primary stapling. This study was conducted in the European Union (EU) between

November 2000 and March 2002. The objective of the study was to compare efficacy and safety of TachoSil versus standard surgical treatment as secondary management of intraoperative pulmonary air leakage after lobectomy in lung cancer patients.

A total of 96 patients were treated with TachoSil and 93 with standard surgical treatment. Subjects were adults who were undergoing planned lobectomy for lung cancer and developed air leakage after lobectomy.

The primary endpoint for efficacy was the incidence of air leakage 42-54 hours after surgery. Secondary endpoints were reduction of intra-operative air leakage intensity after the first test treatment, intensity and duration of post-operative air leakage, and duration of post-operative chest tube drainage up to 9 days after surgery. The primary null hypothesis was tested by use of Fisher's exact test. Sample size calculation was based on the primary efficacy endpoint and designed to detect a difference in success rates of 60% and 80% for standard treatment and TachoSil, respectively. This yielded a sample size of approximately 160 patients.

Results of this study are included below.

Table 3. Primary Endpoint. Incidence of air leakage 48 h after surgery. Stratified analysis. Intent-to-Treat (ITT) population.

Controlling for grade of air leakage intensity at randomisation

	Grade 0 at randomisation				Grade 1-2 at randomisation			
	TachoComb S		Standard		TachoComb S		Standard	
	N	%	N	%	N	%	N	%
Present	15	30.0	13	26.0	18	39.1	21	48.8
Not present	35	70.0	37	74.0	28	60.9	20	46.5
Missing	-	-	-	-	-	-	2	4.7
All	50	100.0	50	100.0	46	100.0	43	100.0

In the statistical analysis the 2 missing values are set to 'Not present'

Randomisation stratum 0 (Intra-operative air leakage intensity grade 0 at randomisation), Fisher's Exact Test: p=0.8240

Randomisation stratum 1-2 (Intra-operative air leakage intensity grade 1-2 at randomisation), Fisher's Exact Test: p=0.2866

Cochran-Mantel-Haenszel Test controlling for randomisation stratum: Test statistic=0.2498, df=1, p=0.6172

Odds ratio of Incidence of air leakage in the TachoComb S treatment group in relation to the Standard treatment group:
Randomisation stratum 0: OR=1.22 95% exact confidence interval: 0.46 to 3.22
Randomisation stratum 1-2: OR=0.61 95% exact confidence interval: 0.24 to 1.56

Table 4. Primary Endpoint. Incidence of air leakage 48 h after surgery. Stratified analysis. Per Protocol population (PP).

Controlling for grade of air leakage at randomisation

Air Leakage	Grade 0 at randomisation				Grade 1-2 at randomisation			
	TachoComb S		Standard		TachoComb S		Standard	
	N	%	N	%	N	%	N	%
Present	13	27.7	11	25.6	18	41.9	18	52.9
Not present	34	72.3	32	74.4	25	58.1	16	47.1
All	47	100.0	43	100.0	43	100.0	34	100.0

Randomisation stratum 0 (Intra-operative air leakage intensity grade 0 at randomisation), Fisher's Exact Test: p=1.0000

Randomisation stratum 1-2 (Intra-operative air leakage intensity grade 1-2 at randomisation), Fisher's Exact Test: p=0.3655

Cochran-Mantel-Haenszel Test controlling for randomisation stratum: Test statistic=0.2904, df=1, p=0.5899

Odds ratio of Incidence of air leakage in the TachoComb S treatment group in relation to the Standard treatment group:
Randomisation stratum 0: OR=1.11 95% exact confidence interval: 0.39 to 3.18
Randomisation stratum 1-2: OR=0.64 95% exact confidence interval: 0.23 to 1.74

Table 5. Reduction in intraoperative air leakage intensity. ITT population.

Intensity before randomisation - Intensity after first test treatment

Reduction in intraoperative air leakage intensity	TachoComb S		Standard	
	N	%	N	%
Missing	-	-	11	11.8
-1	1	1.0	4	4.3
0	61	63.5	56	60.2
1	19	19.8	15	16.1
2	15	15.6	7	7.5
All	96	100.0	93	100.0

Mann-Whitney test: p=0.0968

Table 6. Reduction in intraoperative air leakage intensity. PP population.

Intensity before randomisation - Intensity after first test treatment

Reduction in intraoperative air leakage intensity	TachoComb S		Standard	
	N	%	N	%
Missing	-	-	10	13.0
-1	1	1.1	2	2.6
0	57	63.3	45	58.4
1	18	20.0	13	16.9
2	14	15.6	7	9.1
All	90	100.0	77	100.0

Mann-Whitney test: p=0.8379

Table 7. Intraoperative intensity of air leakage. Cross-tabulation. ITT population.

Before randomisation and after first test treatment

Before randomisation	After 1st test treatment											
	TachoComb S						Standard					
	No test	Absent	Mild	Moderate	Severe	All	No test	Absent	Mild	Moderate	Severe	All
Absent	-	49	1	-	-	50	11	37	2	-	-	50
Mild	-	8	5	-	-	13	-	7	11	1	-	19
Moderate	-	15	11	7	-	33	-	7	8	8	1	24
All	-	72	17	7	-	96	11	51	21	9	1	93

Table 8. Reduction in intraoperative air leakage intensity (subgroup analysis). ITT population.

Patients entering the trial with intensity grade > 0
Intensity before randomisation - Intensity after first test treatment

Reduction in intraoperative air leakage intensity	TachoComb S		Standard	
	N	%	N	%
-1	-	-	2	4.7
0	12	26.1	19	44.2
1	19	41.3	15	34.9
2	15	32.6	7	16.3
All	46	100.0	43	100.0

Mann-Whitney test: p=0.0148

Table 9. Reduction in intraoperative air leakage intensity (subgroup analysis). PP population.

Patients entering the trial with intensity grade > 0
Intensity before randomisation - Intensity after first test treatment

Reduction in intraoperative air leakage intensity	TachoComb S		Standard	
	N	%	N	%
-1	-	-	1	2.9
0	11	25.6	13	38.2
1	18	41.9	13	38.2
2	14	32.6	7	20.6
All	43	100.0	34	100.0

Mann-Whitney test: p=0.1120

For the primary endpoint, incidence of air leakage 42-54 hours after surgery, results were 34% for TachoSil and 37% for standard treatment (p=0.76), irrespective of degree of air leakage at randomisation. No significant findings were noted for the secondary efficacy endpoints, except reduction of intra-operative air leakage in the ITT group with air-leakage Grade 1-2, which was significantly higher for TachoSil than for standard treatment (p=0.015).

Study TC-014-IN

This study was an open, randomised, prospective, multicentre, parallel-group Phase III trial to compare haemostatic efficacy and safety of TachoSil and argon beamer in patients undergoing **liver resection**. This study was conducted in the EU between April 2001 and April 2002.

The objective of the study was to compare haemostatic efficacy and safety of TachoSil and argon beamer in patients undergoing liver resection. A total of 59 patients received TachoSil and 62 patients underwent argon beamer application. Subjects were adults undergoing planned elective liver resection for any reason, who developed minor or moderate haemorrhage persisting after primary surgical haemostatic procedures of the major vessels following at least segmental resection.

The primary efficacy endpoint was time to intra-operative haemostasis after application of TachoSil or argon beamer. Secondary endpoints were proportion of patients with haemostasis 10 min after initiation of test treatment without additional haemostatic measures, volume and haemoglobin concentration of drainage fluid at Days 1-2 after

surgery and total post-operative duration of drainage. The primary endpoint was subject to an explorative parametric survival analysis that took account of interval censoring. The sample size calculation was based on the primary endpoint, with 107 patients being required for a power of 80%.

Results of this study are included below.

Table 10. Primary Endpoint. Time to haemostasis. ITT population.

	TachoCo-mb S	Argon beamer
N	59	62
Mean	3.9	6.3
Std	2.8	6.2
Min	3	3
Median	3.0	4.0
Max	20	39

Table 11. Time to haemostasis. Results of exploratory analysis. ITT population.

Mean time to haemostasis for TachoComb S in relation to mean time to haemostasis for Argon beamer

	TachoComb S / Argon beamer			
	Estimate	CI lower	CI upper	P-value of Treatment effect
Tmt	0.38	0.22	0.68	0.0009
Tmt Centre*	0.55	0.37	0.82	0.0036

* Testing Centre effect: p<0.0001 (p=2.3922283E-8)

Table 12. Haemostasis before/at 10 min. ITT population.

Haemostasis	TachoComb S		Argon beamer	
	N	%	N	%
Before/at 10 minutes	57	96.6	56	90.3
After 10 minutes	2	3.4	6	9.7
All	59	100.0	62	100.0

Fisher's Exact Test: p=0.2786

Table 13. Volume and haemoglobin concentration of drainage. Analysis of variance. ITT population.

Mean estimate in TachoComb S treatment group in percent of mean estimate in Argon beamer treatment group

	TachoComb S / Argon beamer			
	Estimate	CI lower	CI upper	P-value of Treatment effect
Drainage (ml)				
24 hours	120%	82%	176%	0.3213
48 hours	128%	88%	187%	0.1837
Haemoglobin (mmol/L)				
24 hours	79%	50%	125%	0.3210
48 hours	50%	30%	85%	0.0117

For the primary endpoint, mean time to haemostasis was 3.9 min (median 3.0, range 3-20) for TachoSil and 6.3 min (median 4.0, range 3-39) with argon beamer (p=0.0007). There was no significant difference between treatment groups for volume of drainage at Day 1 and Day 2 after surgery. Statistically significant results were seen for haemoglobin concentration of drainage fluid 48 hours post surgery in favour of TachoSil (p=0.012) and for duration of drainage in favour of argon beamer (p=0.005). No significant safety issues were identified.

Study TC-015-IN

This study was an open, randomised, prospective, multicentre, parallel-group Phase III trial to compare efficacy and safety of TachoSil versus standard treatment in patients undergoing surgical **resection of superficial renal tumour**. This study was conducted in the EU between September 2002 and October 2004.

The objective of the study was to compare efficacy and safety of TachoSil and standard surgical treatment (suturing) for the control of local bleeding in patients undergoing surgical resection of renal tumours. A total of 92 patients received TachoSil and 93 patients received standard surgical treatment. Subjects were adults planned for open surgery of superficial tumour, with resection wound suited for treatment with either TachoSil or standard treatment.

The primary efficacy endpoint was intra-operative time to haemostasis, with secondary efficacy endpoints of proportion of subjects with haemostasis 10 min after trial treatment, and occurrence of haematoma on day 2 after surgery. The sample size calculation was based on the primary endpoint, with 170 subjects being required for a power of 90% and a significance level of 5%.

Results of this study are included below.

Table 14. Time used for primary haemostasis (minutes). ITT population.

	TachoComb S	Standard	All
Time used for primary haemostasis			
N	92	93	185
Missing	0	0	0
Mean	8.5	8.4	8.5
Std	5.8	5.0	5.4
Min	0	0	0
Median	7.0	7.0	7.0
Max	26	21	26

Table 15. Primary endpoint. Obtained values of time to haemostasis (minutes). ITT population.

Minutes= . is a missing value.

	TachoComb S		Standard	
	N	%	N	%
Minutes				
.	1	1.1	1	1.1
3	48	52.2	10	10.8
4	7	7.6	6	6.5
5	11	12.0	7	7.5
8	11	12.0	26	28.0
9	2	2.2	5	5.4
10	5	5.4	8	8.6
11	1	1.1	2	2.2
12	-	-	5	5.4
13	1	1.1	8	8.6
14	1	1.1	3	3.2
15	1	1.1	4	4.3
16	2	2.2	-	-
17	1	1.1	2	2.2
18	-	-	1	1.1
20	-	-	2	2.2
21	-	-	1	1.1
25	-	-	1	1.1
27	-	-	1	1.1
All	92	100.0	93	100.0

Minutes= . has been used where there a missing value.

Table 16. Time to haemostasis. Results of exploratory analysis. ITT population.

Mean time to haemostasis for TachoComb S in relation to mean time to haemostasis for Standard

	TachoComb S / Standard				
	Estimate	95% CI lower	95% CI upper	P-value of Treatment effect	P-value of Centre effect
Treat	0.35	0.25	0.50	<.0001	-
Treat Centre	0.34	0.24	0.46	<.0001	<.0001

Table 17. Haemostasis before/at 10 minutes. ITT population.

	TachoComb S		Standard	
	N	%	N	%
Graz				
Before/at 10 minutes	9	100.0	3	42.9
After 10 minutes	-	-	4	57.1
All	9	100.0	7	100.0
Salzburg/Wien				
Before/at 10 minutes	2	50.0	4	80.0
After 10 minutes	2	50.0	1	20.0
All	4	100.0	5	100.0
Leuven				
Before/at 10 minutes	21	100.0	17	89.5
After 10 minutes	-	-	2	10.5
All	21	100.0	19	100.0
Wilhemshaven				
Before/at 10 minutes	4	100.0	4	66.7
After 10 minutes	-	-	2	33.3
All	4	100.0	6	100.0
Tübingen				
Before/at 10 minutes	10	100.0	7	53.8
After 10 minutes	-	-	6	46.2
All	10	100.0	13	100.0
Homburg/Saar				
Before/at 10 minutes	17	81.0	11	57.9
After 10 minutes	4	19.0	8	42.1
All	21	100.0	19	100.0

	TachoComb S		Standard	
	N	%	N	%
Hannover S				
Before/at 10 minutes	7	87.5	4	50.0
After 10 minutes	1	12.5	4	50.0
All	8	100.0	8	100.0
Coburg				
Before/at 10 minutes	6	100.0	3	60.0
After 10 minutes	-	-	2	40.0
All	6	100.0	5	100.0
Lei/Ham/Ess/Pla				
Before/at 10 minutes	8	100.0	9	90.0
After 10 minutes	-	-	1	10.0
All	8	100.0	10	100.0
All				
Before/at 10 minutes	84	92.3	62	67.4
After 10 minutes	7	7.7	30	32.6
All	91	100.0	92	100.0

Table 18. Haemostasis before/at 10 minutes-Analysis. ITT population.

	Chi-square	Df	P-value
Fisher's Exact Test	-	-	<.0001
Breslow-Day test for homogeneity of odds ratios	11.578	8	0.1710
Cochran-Mantel-Haenszel Test	18.096	1	<.0001

Table 19. Sonography. Haematoma formation. ITT population.

	TachoComb S		Standard		All	
	N	%	N	%	N	%
NO SIGN	69	75.0	67	72.0	136	73.5
MINIMAL	12	13.0	18	19.4	30	16.2
CLEARLY DEFINED < 5 CM	5	5.4	2	2.2	7	3.8
CLEARLY DEFINED > 5 CM	3	3.3	2	2.2	5	2.7
NOT DONE	2	2.2	4	4.3	6	3.2
MISSING	1	1.1	.	.	1	0.5
All	92	100.0	93	100.0	185	100.0

Mann-Withney Test of Equality over Treatments:
p=0.8677

Table 20. Drainage 24 h postoperatively. ITT population.

	TachoComb S	Standard	All
Volume of drainage (ml)			
N	89	93	182
Missing	3	0	3
Mean	187.7	173.6	180.5
Std	178.40	175.41	176.53
Min	0.0	0.0	0.0
Median	150.0	130.0	150.0
Max	1000.0	1260.0	1260.0
Duration of drainage (hours)			
N	90	93	183
Missing	2	0	2
Mean	22.5	22.5	22.5
Std	4.56	6.18	5.43
Min	14.2	12.4	12.4
Median	22.3	21.1	21.8
Max	37.1	37.7	37.7
Haemoglobin concentration (g/dl)			
N	74	74	148
Missing	18	19	37
Mean	4.2	4.2	4.2
Std	4.34	3.56	3.95
Min	0.1	0.1	0.1
Median	2.8	3.2	3.1
Max	26.9	17.6	26.9

For the primary efficacy endpoint, the average (median) time to haemostasis was 5.3 (3.0) minutes for TachoSil and 9.5 (8.0) minutes for standard treatment (p<0.0001). Haemostasis before/ at 10 min was obtained in 84 (92%) TachoSil and in 62 (67%) standard treatment subjects (p<0.0001). Haematoma on Day 2 was reported in 20/89 TachoSil subjects and 22/89 standard treatment subjects.

Study TC-016-IN

This study was an open, randomised, prospective, multicentre, parallel-group Phase III trial to compare haemostatic efficacy and safety of TachoSil and argon beam coagulator treatment in patients undergoing **liver resection**. This study was conducted in the EU between March 2003 and August 2003.

The objective of the study was to compare the efficacy and safety of TachoSil and argon beamer treatment for control of local bleeding in subjects undergoing surgical resection of the liver. A total of 60 subjects received TachoSil and 59 received argon beamer treatment. Subjects were adults undergoing planned elective liver resection for any reason, who developed minor or moderate haemorrhage persisting after primary surgical haemostatic procedures of the major vessels following at least segmental resection.

The primary efficacy endpoint was time to intra-operative haemostasis after application of TachoSil or argon beamer. Secondary endpoints were total drain volume, total postoperative duration of drainage, haemoglobin concentration of drainage fluid at Days 1-2 after surgery and on the day of drain removal, and bilirubin concentration of drainage fluid at Days 1-2 after surgery and on the day of drain removal. The sample size calculation was based on the primary endpoint, with 120 subjects being required for a power of 90% and a significance level of 5%.

Results of this study are included in Tables 21-23 below.

For the primary efficacy endpoint, the average (median) time to haemostasis was 3.6 min (3.0, range 3-8 min) for TachoSil and 5.0 min (3.0, range 3-23 min) for argon beamer treatment (p=0.0018). Mean total drain volume was 3.1 litres for TachoSil and 4.1 litres for argon beamer (p=0.19). Mean postoperative duration of drainage was 6.6 days for TachoSil and 7.6 days for argon beamer subjects (p=0.32). There was no significant difference between groups for the other secondary endpoints.

Study TC-021-IM

This study was an open, randomised, prospective, multicentre, parallel-group Phase IIIb trial to compare efficacy and safety of TachoSil versus standard surgical treatment in patients undergoing **lobectomy for lung cancer** and requiring treatment for air leakage. This study was conducted in the EU between January 2006 and March 2007.

The objective of the study was to compare sealing and safety of TachoSil versus standard surgical treatment as secondary management of intraoperative pulmonary air leakage after lobectomy in patients with lung malignancies with or without metastases. A total of 148 patients were treated with TachoSil and 151 with standard surgical treatment. Subjects were adults who were undergoing planned lobectomy for lung cancer with or without metastases and developed intra-operative air leakage after lobectomy.

The primary endpoint for efficacy was the duration of post-operative air leakage. The secondary endpoint was reduction in intra-operative air leakage intensity. The sample size calculation was based on the primary endpoint, with 300 subjects being required for a power of 94% and a significance level of 5%.

Results of this study are included in Tables 24-28 below.

Table 21. Primary endpoint: Time to Haemostasis (minutes). ITT Population

	TachoComb S		Argon beamer	
	n	%	n	%
N	60	100.0	59	100.0
Time to haemostasis (minutes)				
Missing*	0	0.0	0	0.0
[0-3)	39	65.0	32	54.2
[3-4)	12	20.0	6	10.2
[4-5)	8	13.3	9	15.3
[5-8)	1	1.7	5	8.5
[8-9)	0	0.0	2	3.4
[9-10)	0	0.0	2	3.4
[10 or more)	0	0.0	3	5.1
Mean time if > 10 minutes			17.0	
Minimum	3		3	
Median**	3		3	
Maximum	8		23	

Table 22. Time to Haemostasis (minutes)Life Table Estimates. ITT Population

	TachoComb S						Argon beamer					
	Effective sample size for the interval	Number with haemostasis at end of interval	Number censored	Survival	Failure	Survival standard error	Effective sample size for the interval	Number with haemostasis at end of interval	Number censored	Survival	Failure	Survival standard error
Time to haemostasis (minutes)												
	60	0	0	1.0000	0.0000	0.0000	59	0	0	1.0000	0.0000	0.0000
[0-3)	60	39	0	0.3500	0.6500	0.0616	59	32	0	0.4576	0.5424	0.0649
[3-4)	21	12	0	0.1500	0.8500	0.0461	27	6	0	0.3559	0.6441	0.0623
[4-5)	9	8	0	0.0167	0.9833	0.0165	21	9	0	0.2034	0.7966	0.0524
[5-8)	1	1	0	0.0000	1.0000	0.0000	12	5	0	0.1186	0.8814	0.0421
[8-9)	0	0	0				7	2	0	0.0847	0.9153	0.0363
[9-10)	0	0	0				5	2	0	0.0508	0.9492	0.0286
[10 or more)	0	0	0				3	3	3			
Test of equality over treatments:												
Chi-Square	9.7417											
Degrees of freedom	1											
p-Value	0.0018											

Table 23. Total postoperative duration of drainage (days). Life Table Estimates.

Population: ITT

	TachoComb S						Argon beamer					
	Effective sample size for the interval	Number with drains removed at end of interval	Number censored	Survival	Failure	Survival standard error	Effective sample size for the interval	Number with drains removed at end of interval	Number censored	Survival	Failure	Survival standard error
Duration of drainage (days)												
	59	0	0	1.0000	0.0000	0.0000	59	0	0	1.0000	0.0000	0.0000
[0-1)	59	0	0				59	0	0			
[1-2)	59	2	0	0.9661	0.0339	0.0236	59	0	0			
[2-3)	57	9	0	0.8136	0.1864	0.0507	59	6	0	0.8983	0.1017	0.0393
[3-4)	48	2	0	0.7797	0.2203	0.0540	53	11	0	0.7119	0.2881	0.0590
[4-5)	46	12	0	0.5763	0.4237	0.0643	42	5	0	0.6271	0.3729	0.0630
[5-6)	34	6	0	0.4407	0.5593	0.0646	37	8	0	0.4915	0.5085	0.0651
[6-7)	26	6	1	0.3559	0.6441	0.0623	29	5	0	0.4068	0.5932	0.0640
[7-8)	20	4	0	0.2847	0.7153	0.0592	24	4	0	0.3390	0.6610	0.0616
[8-9)	16	3	0	0.2314	0.7686	0.0555	20	3	0	0.2881	0.7119	0.0590
[9-10)	13	3	0	0.1780	0.8220	0.0505	17	6	1	0.2034	0.7966	0.0524
[10-11)	10	1	0	0.1602	0.8398	0.0485	11	1	0	0.1849	0.8151	0.0508
[11-12)	9	1	0	0.1424	0.8576	0.0463	10	2	0	0.1479	0.8521	0.0469
[12-13)	8	1	0	0.1246	0.8754	0.0438	8	1	0	0.1294	0.8706	0.0445
[13-14)	7	0	0				7	0	0			
[14-21)	7	5	0	0.0356	0.9644	0.0247	7	3	0	0.0740	0.9260	0.0351
[21 or more)	2	2	0	0.0000	1.0000	0.0000	4	4	1	0.0000	1.0000	0.0000

Test of equality over treatments:	
Chi-Square	0.9894
Degrees of freedom	1
p-value	0.3199
Treatment p-value adjusted for:	
SFChem	0.3987
KlatRLH	0.3448

Table 24. Duration of intra-operative air leakage. Life Table Estimates. ITT population.

% of patients with post-opearative air leakage at selected assessments by centre and treatment

	Tachosil (N=148)							Standard (N=151)						
Centre	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M	Day0 E	Day1 M	Day1 E	Day2 E	Day5 M	Day10 M	Day20 M
Vienna	67	33	29	10	5	5	0	86	67	48	24	10	0	0
Leuven	40	40	40	20	0	0	0	67	67	67	33	0	0	0
Zürich	67	33	33	0	0	0	0	50	0	0	0	0	0	0
Heidelberg	53	35	35	18	6	6	6	35	29	24	18	6	0	0
Essen	43	43	43	43	29	14	0	57	57	57	43	14	14	14
Freiburg	69	69	46	31	23	15	8	71	43	43	29	7	7	0
Odense	83	78	72	67	22	6	0	100	88	59	47	35	12	0
Budapest	40	33	13	7	0	0	0	60	53	47	13	7	0	0
Milano	100	100	100	38	0	0	0	100	100	92	58	33	33	0
Padova	77	46	46	31	8	0	0	73	60	53	40	33	13	0
Rome	59	53	41	12	0	0	0	53	53	47	32	21	16	5
Göteborg	67	67	67	33	0	0	0	82	20	20	0	0	0	0
All	66	53	47	27	8	4	2	71	59	49	31	17	8	2

Log-Rank test of equality over treatments stratified by centre:
N=299, Chi-Square=4.7887, df= 1, p=0.0286

Table 25. Duration of postoperative air leakage. Parametric Analysis. ITT population.

Assumed distribution: weibull

N=299

Scale	Effect	Estimate (se)	95% CI Lower	95% CI Upper	Chi-Sq	df	P-value
Log-time	Standard-Tachosil	0.3101 (0.217)	-0.12	0.74	2.038	1	0.1534

Table 26. Duration of postoperative air leakage. Parametric Analysis. PP population.

Assumed distribution: weibull

N=278

Scale	Effect	Estimate (se)	95% CI Lower	95% CI Upper	Chi-Sq	df	P-value
Log-time	Standard-Tachosil	0.4356 (0.205)	0.03	0.84	4.493	1	0.0340

Table 27. Reduction in intraoperative air leakage intensity. ITT population.

Wilcoxon's rank sum test (using Normal approximation):

STANDARD: Score= 19885 n=145
TACHOSIL: Score= 22898 n=147 z-value=-2.0333 p-value=0.0420

Air Grade Reduction	TACHOSIL N	TACHOSIL %	STANDARD N	STANDARD %	All N	All %
0	42	28.6	55	37.9	97	33.2
1	69	46.9	66	45.5	135	46.2
2	36	24.5	24	16.6	60	20.5
All	147	100.0	145	100.0	292	100.0

Table 28. Volume of daily postoperative chest tube drainage (mL). ITT population.

Site = Total

	TACHOSIL						STANDARD					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
DAY 1	147	538.4	272.4	500	40	1600	150	518.4	288.7	480	0	2270
DAY 2	143	457.7	256.2	400	80	1530	146	394.8	217.1	358	30	1350
DAY 3	111	322.3	271.0	265	0	1930	125	298.3	169.4	260	0	980
DAY 4	49	300.4	156.3	260	50	750	60	252.0	140.1	220	0	600
DAY 5	36	277.1	130.3	260	50	560	47	278.6	143.9	260	0	900
DAY 6	22	252.7	171.0	228	70	665	33	242.3	132.3	220	0	600
DAY 7	13	345.4	179.4	300	100	710	20	231.8	127.5	228	0	550
DAY 8	8	288.1	257.1	230	10	870	15	199.3	136.4	150	0	500
DAY 9	8	241.3	252.9	200	0	820	12	218.8	120.3	198	0	440
DAY 10	6	189.2	78.9	195	55	260	9	167.8	93.0	200	0	260
DAY 11	4	135.0	124.5	130	0	280	7	174.3	107.5	150	0	350
DAY 12	3	210.0	69.3	250	130	250	5	150.0	101.0	180	0	250
DAY 13	2	75.0	35.4	75	50	100	4	156.3	129.7	175	0	275
DAY 14	1	50.0	-	50	50	50	5	108.0	111.0	100	0	240
DAY 15	1	0.0	-	0	0	0	4	157.5	81.0	150	80	250
DAY 16	1	420.0	-	420	420	420	2	135.0	91.9	135	70	200
DAY 17	0	-	-	-	-	-	2	150.0	141.4	150	50	250
DAY 18	-	-	-	-	-	-	2	300.0	70.7	300	250	350
DAY 19	-	-	-	-	-	-	2	60.0	14.1	60	50	70
DAY 20	-	-	-	-	-	-	2	250.0	113.1	250	170	330
DAY 21	-	-	-	-	-	-	1	100.0	-	100	100	100
DRAIN REMOVAL	143	282.4	292.9	170	0	2330	136	168.9	120.5	150	0	617

For the primary efficacy endpoint, the primary analysis showed that subjects in the TachoSil group recovered at a higher rate than did standard treatment subjects (p=0.030). The exploratory parametric analysis showed an overall estimated median time to cessation of air leakage of 14.5 hours for TachoSil and 19.5 hours for standard treatment (p=0.153). For the secondary efficacy endpoint, 71 % of TachoSil subjects achieved a reduction of 1 or 2 grades compared with 62% in the standard treatment group (p=0.042).

Study TC-023-IM

This study was a randomised, open label, parallel-group, multi-centre trial to compare the efficacy and safety of TachoSil versus standard haemostatic treatment in **cardiovascular surgery**. This study was conducted in the EU between June 2006 and September 2007.

The objective of the study was to demonstrate efficacy and safety of TachoSil in cardiovascular surgery. A total of 59 patients received TachoSil and 60 patients received standard treatment. Subjects were adults who were planned for elective surgery on the heart, ascending aorta or arch, requiring cardiopulmonary bypass, who developed bleeding from the surgical site requiring supportive haemostatic treatment.

The primary efficacy endpoint was the proportion of subjects achieving haemostasis after 3 min/6 min (ITT). Other variables included duration of drainage, post-operative drainage volume and post-operative transfusions. The sample size calculation was based on the primary endpoint, with 120 subjects being required for a power of 90% and a significance level of 5%.

Results of this study are included below.

Table 29a. Primary endpoint. Proportion of subjects achieving haemostasis after 3 minutes. ITT population.

Cochran-Mantel-Haenszel test stratifying by centre testing for association between treatment and haemostasis at 3 minutes

Treatment	Total number of patients	Proportion, p, with haemostasis	95% CI for p	P-value
TACHOSIL	59	0.746	[0.635; 0.857]	<.0001
STANDARD	60	0.333	[0.214; 0.453]	.

Breslow-Day test for homogeneity of odds ratios across centres:
Chi-Square= 0.248, df= 4, p=0.993

Table 29b. Primary endpoint. Proportion of subjects achieving haemostasis after 3 minutes. PP population.

Cochran-Mantel-Haenszel test stratifying by centre testing for association between treatment and haemostasis at 3 minutes

Treatment	Total number of patients	Proportion, p, with haemostasis	95% CI for p	P-value
TACHOSIL	59	0.746	[0.635; 0.857]	<.0001
STANDARD	52	0.346	[0.217; 0.475]	.

Breslow-Day test for homogeneity of odds ratios across centres:
Chi-Square= 0.659, df= 4, p=0.956

Table 30. Secondary endpoint. Proportion of subjects achieving haemostasis after 6 minutes. ITT population.

Cochran-Mantel-Haenszel test stratifying by centre testing for association between treatment and haemostasis at 6 minutes

Treatment	Total number of patients	Proportion, p, with haemostasis	95% CI for p	P-value
TACHOSIL	59	0.949	[0.893; 1.000]	0.0006
STANDARD	60	0.717	[0.603; 0.831]	.

Breslow-Day test for homogeneity of odds ratios across centres:
Chi-Square= 4.378, df= 4, p=0.357

Table 31. Duration of drainage (hours). ITT population.

Number of hours from end of surgery until time of drain removal

	N	Missing	Mean	Median	SD	Min	Max
TACHOSIL	56	3	93	46	177	18	1093
STANDARD	58	2	67	44	106	15	687
TOTAL	114	5	80	45	145	15	1093

Table 32. Total volume of postoperative drainage (mL). ITT population.

	N	Mean	SD	Median	Min	Max
TACHOSIL	59	1005	1128	600	75	5240
STANDARD	60	932	1320	498	100	9100
Total	119	968	1224	550	75	9100

For the primary efficacy endpoint, the proportion (95% confidence interval (CI)) of subjects with haemostasis at 3 min was 0.75 (0.64-0.86) for TachoSil and 0.33 (0.21-0.45) for standard treatment (p<0.0001). For the proportion of subjects achieving haemostasis, the respective figures were 0.95 (0.89-1.0) for TachoSil and 0.72 (0.60-0.83) for standard treatment (p=0.0006).

Clinical studies in special populations

Study TC-019-IN was a prospective, multicentre, Phase IIIb study of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. This study was conducted in the UK between May 2006 and July 2007.

The objective of the study was to collect data on efficacy (intra-operative haemostasis) and safety of TachoSil as treatment to control local bleeding in children undergoing surgical resection of the liver with or without segmental transplantation. While the study was planned for 40 subjects, the study was abandoned after only 16 patients had been enrolled. Subjects were children between 4 weeks and 6 years who were planned for at least segmental resection of the liver or resection followed by placement of a segmental liver graft, who developed minor or moderate haemorrhage after primary surgical haemostatic procedures of major vessels.

The primary efficacy endpoint was time to intra-operative haemostasis after the application of TachoSil . The original sample size was based on the primary efficacy endpoint and a sample size of 40 was chosen based on 95% CI of 0.76-0.97. Descriptive statistics only were performed.

Conduct of the study was complicated by issues surrounding the clinical management of severely ill children, violation of inclusion/ exclusion criteria and discontinuation in 2 cases. None of these factors were related to the investigational product. A total of 13 subjects (81.3% (95% CI 61.8-100)) obtained haemostasis at 3 min, one after 8 min and 2 failed and required other measures. There were no safety issues identified as being related to TachoSil.

Analysis performed across trials (pooled analyses and meta-analysis)

Results from the haemostasis studies (TC-014-IN, TC-015-IN, TC-016-IN and TC-023-IM) were pooled for further analysis. However, time to haemostasis data were available for the liver and kidney trials only and the estimated median time to haemostasis for this data pool showed a notable difference (3.0 and 5.0 minutes, respectively, for TachoSil and the comparator). In the overall haemostasis trial pool, 64.4% of TachoSil patients compared to 33.6% of comparator patients achieved haemostasis at 3 minutes. It should be noted however that data could not be pooled from all haemostasis studies. Pooled haemostasis analysis is included below.

Table 33. Median time to haemostasis (minutes) by organ and treatment. Pooled Haemostasis trials TC-014-IN, TC-015-IN and TC-016-IN. ITT population.

	TachoSil N = 211		Comparator Treatment N = 214		Treatment Difference[a]
	Estimated Median Time (min)	95% CI	Estimated Median Time (min)	95% CI	Hazard Ratio
Overall	3.0	(NC, NC)	5.0	(5.0–8.0)	2.665
Kidney	3.0	(3.0–5.0)	8.0	(8.0–10.0)	3.440
Liver	3.0	(NC, NC)	3.0	(3.0–4.0)	2.554

CI, confidence interval; NC, not calculable.
Note: Median times are displayed for time to haemostasis using Kaplan-Meier estimates, stratified by organ and treatment. Quantiles are reported as NC if the relevant sample statistic is based on a censored value. Confidence limits are also reported as NC if the width of the half-interval would be zero. Results do not include trial TC-023-IM as data were not recorded in a manner suitable for pooling.
[a] Hazard ratios are from a proportional hazards model.

Table 34. Duration of postoperative fluid drainage (days) by treatment and trial. Haemostasis trials TC-014-IN and TC—016-IN. ITT Population.

	TC-014-IN		TC-016-IN	
	TachoSil N = 59	CT N = 62	TachoSil N = 60	CT N = 59
n	59	62	59	59
Median[a]	6.0	5.1	5.0	5.0
Mean (SD)	8.2 (6.0)	5.7 (2.9)	6.6 (5.1)	7.6 (6.8)
Min–Max	2–27	2–15	1–28	2–38
p-value[b]	p=0.005		p=0.320	

CT, comparator treatment.
[a] Median calculated from survival analysis.
[b] The p-value is from the log-rank test.

Table 35. Median postoperative drainage duration (days) overall by treatment and by organ. Log Rank test results. Pooled Haemostasis trials TC-014-IN, TC-016-IN and TC-023-IM. ITT population.

	TachoSil N = 178		Comparator Treatment N = 181		Treatment Difference[a]
	Estimated Median Time (days)	95% CI	Estimated Median Time (days)	95% CI	Hazard Ratio
Overall	5.0	(5.0-6.0)	5.0	(4.0-6.0)	0.799
Cardiovascular	3.0	(NC, NC)	3.0	(NC, NC)	0.774
Liver	6.0	(6.0-8.0)	6.0	(6.0-7.0)	0.755

CI, confidence interval; NC, not calculable.
[a] Hazard ratios are from a proportional hazards model.
Note: Median times are displayed for duration of post-operative drainage using Kaplan-Meier estimates, stratified by organ and treatment. Quantiles are reported as NC if the relevant sample statistic was based on a censored value. Confidence intervals are also potentially reported as NC if the width of the half-interval would be zero.
Data from the kidney trial TC-015-IN was not included since duration of post-operative drainage was not recorded.

Table 36. Summary of postoperative drainage fluid (mL) at 24 h after surgery by treatment. Pooled Haemostasis trials TC-014-IN, TC-015-IN and TC-016-IN. ITT population.

	TachoSil N = 211	Comparator Treatment N = 214
N	182	178
Mean	314.4	295.4
SD	383.77	392.89
Median	187.5	180.0
Min–Max	0–3180	0–3000

Note: The 24-hour data were considered to be the drain measurement between 18 and 30 hours.

Table 37. Summary of postoperative drainage fluid (mL) at 24 h and 48 h after surgery by treatment. Pooled Haemostasis trials TC-014-IN and TC-016-IN. ITT population.

	TachoSil N = 119	Comparator Treatment N = 121
Volume of drainage fluid at 24 hours after surgery[a]		
n	93	86
Mean	435.7	424.2
SD	478.45	505.84
Median	240.0	300.0
Min–max	0–3180	0–3000
Volume of drainage fluid at 48 hours after surgery[b]		
n	92	93
Mean	723.3	658.8
SD	749.84	731.81
Median	405.0	410.0
Min–Max	0–3750	7–5000

[a]The 24-hour data were considered to be the drain measurement between 18 and 30 hours.
[b]The 48-hour data were considered to be the drain measurement between 42 and 54 hours.

In addition, results from the lung sealing studies (TC-013-IN and TC-021-IM) were also pooled for analysis. While results favoured TachoSil with regard to reduced intra-operative air leakage intensity and duration of postoperative chest drainage, there were no notable differences between treatments for incidence of air leakage at 48 hours after surgery, volume of postoperative drainage volume or inflation of lung at drain removal. Pooled sealing analysis is included below.

Table 38. Reduction in intraoperative air leakage intensity from baseline by treatment and trail. Lung trials TC-013-IN and TC-021-IM. ITT population.

	TC-013-IN		TC-021-IM	
	TachoSil	CT	TachoSil	CT
Air Grade	N = 46	N = 43	N = 148	N = 151
Reduction	n (%)	n (%)	n (%)	n (%)
n	46	43	147	145
-1	--	2 (4.7)	--	--
0	12 (26.1)	19 (44.2)	42 (28.6)	55 (37.9)
1	19 (41.3)	15 (34.9)	69 (46.9)	66 (45.5)
2	15 (32.6)	7 (16.3)	36 (24.5)	24 (16.6)

CT, comparator treatment.

Table 39. Shift table of reduction in intraoperative air leakage intensity by treatment. Pooled Lung trials TC-013-IN and TC-021-IM. ITT population.

Baseline Air Leakage Intensity Rating[a]		Posttreatment Air Leakage Intensity Rating[b]		
		Grade 0 (absent)	Grade 1 (mild)	Grade 2 (moderate)
	n	n	n	n
TachoSil				
Grade 1 (mild)	91	60	31	0
Grade 2 (moderate)	103	51	27	25
Total	194	111	58	25
Comparator Treatment				
Grade 1 (mild)	89	46	42	1
Grade 2 (moderate)	98	31	35	32
Total	187	77	77	33

Note: Only patients with available data at baseline and posttreatment assessments were included in the analysis.
[a] Baseline intraoperative air leakage intensity is the last measurement taken during surgery before treatment application.
[b] Posttreatment intraoperative air leakage intensity is the measurement taken during surgery after the first application of treatment.

Table 40. Total volume of postoperative chest drainage fluid (mL) by treatment.

Pooled Lung trials TC-013-IN and TC-021-IM. ITT population

	TachoSil N = 195	CT N = 194
Median	1287.5	1370.0
Mean (SD)	1630.8 (1036.64)	1622.3 (996.22)
Min–Max	390–6590	190–5745

CT, comparator treatment; min, minimum; max, maximum.
The total volume of chest drainage fluid was defined as the sum of all drainage up to and including the volume on the day of drain removal.

Table 41. Inflation of lung and number of patients with pneumothroax at chest drain removal by treatment. Pooled Lung trials TC-013-IN and TC-021-IM. ITT population

	TachoSil N = 195 n (%)	Comparator Treatment N = 194 n (%)
Inflation of the lung at drain removal		
Full	131 (67.2)	134 (69.1)
Incomplete	27 (13.8)	32 (16.5)
Collapsed	0	0
Missing	37 (19.0)	28 (14.4)
Patients with pneumothorax at drain removal	38 (19.5)	48 (24.7)

Percentages are based on the number of patients in each treatment group.

Supportive studies

Three uncontrolled studies were also mentioned in the application.

1. TS-001-WE was conducted between 2004 and 2005 on patients who received TachoSil during various surgeries. A total of 154 subjects were enrolled. No further details or results were provided.

2. TC-022-IT was conducted between 2005 and 2007 on patients who received TachoSil during abdominal, urologic and thoracic surgery. A total of 616 subjects were enrolled. No further details or results were provided.
3. TC-027-DE was conducted between 2007 and 2008 on patients who received TachoSil during cholecystectomy. A total of 169 subjects were enrolled. No further details or results were provided.

In addition, mention was also made of 3 ongoing studies.

Evaluator's overall conclusions on clinical efficacy

Guidance on industrially manufactured fibrin sealant products is provided by the TGA adopted EU guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/ Haemostatic Products[1]. This document requires that efficacy has to be assessed in studies with objective clinical endpoints and that clinical studies need to be designed in which the appropriate endpoint is assessed for each therapeutic indication proposed. Such studies also need to be controlled.

Information on clinical efficacy was predominantly provided by 6 pivotal studies, which consisted of 4 studies to investigate haemostatic efficacy and safety of TachoSil (TC-013-IN, TC-015-IN, TC-016-IN and TC-023-IM) and 2 studies to investigate efficacy and safety in air leakage in lung surgery (TC-013-IN and TC-021-IM). These were open-label, multi-centre, randomised, controlled, parallel-group studies that compared TachoSil with surgical standard treatment. The trials were designed with an intra-operative randomisation at the time point during surgery, when a certain pre-defined leakage or bleeding condition was established at the resection wound by the treating surgeon/ investigator. Common and standardised surgical interventions were chosen for the respective trials. Similarly the comparator treatments were chosen according to their standard use in the respective surgical procedure. Efficacy outcome variables were chosen based on their clinical relevance and/or recommendations in regulatory guidelines and appeared to have an appropriate clinical basis. These studies were not designed as non-inferiority or equivalence studies.

With regard to the individual pivotal studies, *TC-014-IN* was designed to assess haemostatic efficacy of TachoSil in patients undergoing liver resection compared to argon beamer. The study was adequately designed and powered to assess the primary efficacy endpoint, which was time to intra-operative haemostasis after application of TachoSil or argon beamer. Results indicated that mean time to haemostasis was 3.9 min (median 3.0, range 3-20) for TachoSil and 6.3 min (median 4.0, range 3-39) with argon beamer ($p=0.0007$).

TC-015-IN was designed to assess haemostatic efficacy of TachoSil in patients undergoing resection of superficial renal tumour, compared to standard surgical treatment (suturing). This study was adequately designed and powered to assess the primary efficacy endpoint, which was intra-operative time to haemostasis after application. For the primary efficacy endpoint, the average (median) time to haemostasis was 5.3 (3.0) for TachoSil and 9.5 (8.0) for standard treatment ($p<0.0001$).

TC-016-IN was designed to assess haemostatic efficacy of TachoSil in patients undergoing liver resection compared to argon beamer. The study was adequately designed and powered to assess the primary efficacy endpoint, which was time to intra-operative haemostasis after application of TachoSil or argon beamer. For the primary efficacy endpoint, the average (median) time to haemostasis was 3.6 min (3.0, range 3-8 min) for TachoSil and 5.0 min (3.0, range 3-23 min) for argon beamer treatment ($p=0.0018$).

TC-023-IM was designed to assess haemostatic efficacy of TachoSil in patients undergoing cardiovascular surgery (requiring cardiopulmonary bypass) compared to haemostatic

fleece. The study was adequately designed and powered to assess the primary efficacy endpoint, which was the proportion of subjects achieving haemostasis after 3 min/6 min (ITT). For the primary efficacy endpoint, the proportion (95% CI) of subjects with haemostasis at 3 min was 0.75 (0.64-0.86) for TachoSil and 0.33 (0.21-0.45) for standard treatment (p<0.0001).

Therefore, for all pivotal trials assessing haemostatic efficacy, the primary efficacy endpoint favoured TachoSil in all four studies. While a pooled analysis supported this, interpretation of this was complicated by the different types of surgery and comparators.

With regard to the individual sealing studies, *TC-013-IN* was designed to assess sealing efficacy of TachoSil in patients undergoing lung lobectomy for lung cancer, compared to standard surgical treatment. The study was adequately designed and powered to assess the primary endpoint for efficacy, which was the incidence of air leakage 42-54 hours after surgery. For the primary endpoint, incidence of air leakage 42-54 hours after surgery, results were 34% for TachoSil and 37% for standard treatment (p=0.76), irrespective of degree of air leakage at randomisation.

TC-021-IM was designed to assess sealing efficacy of TachoSil in patients undergoing lung lobectomy for lung cancer, compared to standard surgical treatment. The primary endpoint for efficacy was the duration of postoperative air leakage. For the primary efficacy endpoint, the primary analysis showed that subjects in the TachoSil group recovered at a higher rate than did standard treatment subjects (p=0.030). The exploratory parametric analysis showed an overall estimated median time to cessation of air leakage of 14.5 hours for TachoSil and 19.5 hours for standard treatment (p=0.153).

Therefore, the results in terms of sealing efficacy from these two trials were less clear-cut than for haemostatic efficacy in terms of comparing TachoSil with standard surgical treatment. While the results were comparable (and generally favoured TachoSil), neither primary efficacy endpoint was significantly in favour of TachoSil. While the pooled analysis favoured TachoSil, interpretation of this was complicated by the different primary efficacy endpoints.

Supporting studies provided little useful additional information on efficacy. Study TC-019-IN was a prospective, multicentre, Phase IIIb study of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. The primary efficacy endpoint was time to intra-operative haemostasis after the application of TachoSil. Unfortunately this study was abandoned prematurely for reasons unrelated to the product and little useful information could be gained. Minimal information was provided on other supporting studies.

Safety

Introduction

Information on clinical safety was collected in all clinical studies, including adverse events and clinical laboratory tests. In addition, information on clinical safety was also available from postmarketing surveillance as well as a review of possible or probable immune-mediated adverse drug reactions.

Study TC-018-IN

There was also one study, TC-018-IN, which specifically assessed safety of TachoSil. This study was an international, non-interventional, prospective, single cohort study of the use of TachoSil in supportive treatment in surgery for improvement of haemostasis where standard treatments are insufficient.

The objective of the study was to collect information on thromboembolic events, immunologic events and drug interactions leading to thromboembolic events or major bleeding occurring within 6 months after exposure to TachoSil. The study was conducted in the EU between June 2005 and July 2008. A total of 3098 patients were identified and analysed in the study, having been prescribed TachoSil for approved indications.

The primary endpoint was the proportion of patients experiencing a thromboembolic event verified by paraclinical examination. Secondary endpoints included the proportion of patients experiencing an immunological event, the proportion of patients experiencing major bleeding requiring interventional treatment, interaction between TachoSil and a drug resulting in a thromboembolic event and the interaction between TachoSil and a drug resulting in a major bleeding. The sample size was based on the expected incidence of thromboembolic events. With 3000 subjects, an observed incidence rate of 10% was estimated with a precision of +/- 1.1%.

Results of this study are included below.

Table 42. Patients with reportable Thromboembolic, Major bleed and Immunological events (N=3098).

	At any time n (%)	On date of surgery n (%)	Between surgery and discharge n (%)	All Related n (%)	All Serious n (%)	All Fatal n (%)
Thromboembolic	46 (1.5)	2 (0.06)	23 (0.7)	3 (0.1)	41 (1.3)	7 (0.2)
Immunological	8 (0.3)	0	5 (0.2)	1 (0.03)	1 (0.03)	0 (0)
Major bleeding	62 (2.0)	24 (0.8)	28 (0.9)	7 (0.2)	55 (1.8)	8 (0.3)

Table 43. Adverse events by System Organ Class and Preferred term.

	All events	Mild events	Moderate events	Severe Events	Related events	Serious events
Thromboembolic events	**51**	**12**	**19**	**20**	**3**	**46**
Deep vein thrombosis	9	5	1	3	-	7
Phlebitis	3	-	3	-	1	3
Other vascular (details in Table 9)	10	2	3	5	-	9
Post-procedural pulmonary embolism	3	-	1	2	1	3
Pulmonary embolism	15	3	6	6	-	14
Pulmonary artery thrombosis	1	-	1	-	-	1
Myocardial infarction	2	-	1	1	-	2
Coronary artery thrombosis	1	-	-	1	-	1
Portal vein thrombosis	2	2	-	-	1	1

Table 43 continued. Adverse events by System Organ Class and Preferred term.

	All events	Mild events	Moderate events	Severe Events	Related events	Serious events
Mesentery artery thrombosis	1	-	-	1	-	1
Mesentery vein thrombosis	1	-	1	-	-	1
Hepatic artery thrombosis	1	-	-	1	-	1
Retinal vein thrombosis	1	-	1	-	-	1
Cerebral artery thrombosis	1	-	1	-	-	1
Immunological events	**9**	**6**	**3**	**-**	**2**	**1**
Rash or rash pruritic	3	3	-	-	-	-
Palmar erythema	1	-	1	-	-	-
Anaphylactic reaction	1	-	1	-	-	-
Drug hypersensitivity	1	1	-	-	-	-
Eosinophilia	1	1	-	-	1	-
Pyrexia	1	1	-	-	1	-
White blood cell count increased	1	-	1	-	-	1
Major bleeding events	**64**	**4**	**27**	**33**	**8**	**57**
Post procedural haemorrhage	21	1	12	8	3	18
Graft haemorrhage	1	-	-	1	-	1
Operative haemorrhage	1	-	-	1	-	1
Subdural haematoma	1	1	-	-	-	1
Haemorrhage (Vascular)	12	-	5	7	1	11
Arterial haemorrhage	6	1	1	4	-	5
Haematoma	4	1	3	-	1	3
Shock haemorrhagic	1	-	-	1	-	1
Wound haemorrhage	1	-	1	-	-	-
	All events	**Mild events**	**Moderate events**	**Severe Events**	**Related events**	**Serious events**
Haemorrhage (Gastrointestinal, details in Table 9)	7	-	2	5	-	7
Haemothorax	4	-	1	3	1	4
Haemoptysis	2	-	-	2	-	2
Splenic haemorrhage	2	-	1	1	1	2
Drug ineffective	1	-	1	-	1	1

A total of 46 patients (1.5%) experienced at least one thromboembolic event, of which 41 patients had a serious thromboembolic event and 2 patients had a serious

thromboembolic event related to TachoSil . A total of 62 patients (2.0%) experienced at least one major bleeding event, of which 55 patients experienced a serious major bleeding event and 7 patients had a serious major bleeding event related to TachoSil. A total of 8 patients (0.3%) experienced at least one immunological event during the study, of which one event was deemed serious and 1 patient had 2 non-serious immunological events related to TachoSil.

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%).[3] Sixteen patients (8.5%) experienced one or more serious adverse events following randomisation, resulting in 19 events and 16 individual SAE reports. 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.

Safety data collected in this study are summarised below.

Table 44a. Adverse events by causality and severity.

Relation to treatment	TachoComb S				Standard treatment			
	Mild	Moderate	Severe	All	Mild	Moderate	Severe	All
Probable	1	-	-	1	1	1	-	2
Possible	3	-	-	3	1	-	-	1
Unlikely	19	2	1	22	1	1	-	2
Not related	10	9	6	25	24	14	3	41
Not assessable	3	2	1	6	20	4	-	24
All	36	13	8	57	47	20	3	70

[3] Sponsor comment: 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, one case of emphysema, was considered related to TachoSil. Additionally, 2 events occurred in 2 patients before randomisation. The only serious adverse event considered related to test treatment (TachoSil) was emphysema. One patient died during screening after a haemorrhage.

Table 44b. Adverse events by System Organ Class.

Number of adverse events	TachoComb S N = 96			Standard treatment N = 93		
By system organ class	n	%	E	n	%	E
All adverse events	39	41	57	42	45	70
Secondary terms - events	11	11	14	17	18	21
Respiratory system disorders	9	9	10	12	13	12
Heart rate and rhythm disorders	8	8	8	10	11	10
Body as a whole, general disorders	4	4	4	10	11	10
Cardiovascular disorders	3	3	3	3	3	4
Urinary system disorders	2	2	2	4	4	5
Gastrointestinal system disorders	3	3	4	1	1	2
Platelet, bleeding and clotting disorders	3	3	3	1	1	1
Resistance mechanism disorders	1	1	1	2	2	2
Metabolic and nutritional system disorders	1	1	1	1	1	1
Central and periph. nervous system disorders	2	2	2	-	-	-
Skin and appendages disorders	2	2	2	-	-	-
Collagen disorders	2	2	2	-	-	-
Psychiatric disorders	1	1	1	-	-	-
Liver and biliary system disorders	-	-	-	1	1	1
Red blood cell disorders	-	-	-	1	1	1

N: Number of patients who received test treatment; n: Number of patients with adverse event;
%: Percentage of patients with adverse event of all treated patients; E: Number of events

Table 45. Serious Adverse Events

System Organ Class	Adverse event	TachoComb S N = 96			Standard N = 93		
		n	%	E	n	%	E
Total	Total	10	10	13	6	6	6
Secondary terms - events	Brain metastases	1	1	1	0	0	0
	Secondary carcinoma	0	0	0	1	1	1
	Surgical site reaction	2	2	3	2	2	2
Respiratory	Bronchitis	1	1	1	0	0	0
	Emphysema	1	1	1	0	0	0
	Pneumonia	0	0	0	2	2	2
	Pulmonary haemorrhage	1	1	1	0	0	0
Heart rate and rhythm	Tachycardia	1	1	1	1	1	1
Cardiovascular, general	Hypertension	1	1	1	0	0	0
Collagen	C-reactive protein positive	1	1	1	0	0	0
Platelet, bleeding and clotting	Embolism pulmonary	1	1	1	0	0	0
Psychiatric	Somnolence	1	1	1	0	0	0
Resistance mechanism	Abscess	1	1	1	0	0	0

TachoSil appeared to be well tolerated and there was no significant difference in safety profile.

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 26 (44%) in the TachoSil group and 24 (39%) in the argon beamer group. The most frequent adverse events were abscess (8 events), fever (7 events), postoperative wound infection (6 events), pneumonia (6 events), cystitis (5 events), urinary tract infection (4 events) and gall bladder disorder (6 events). Four adverse events were considered possibly related to

test treatment.[4] Seventeen adverse events were rated as severe in the TachoSil group compared to 4 in the argon beamer group.

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.[5] Safety data collected in this study are summarised below.

Table 46. Adverse events by System Organ Class.

		TachoComb S			Argon beamer		
		N=59			N=62		
		n	%	E	n	%	E
TOTAL	TOTAL	26	44	50	24	39	47
APPLICATION SITE DISORDERS	TOTAL	-	-	-	1	2	1
	CELLULITIS	-	-	-	1	2	1
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL	4	7	5	7	11	7
	ASCITES	1	2	1	-	-	-
	FATIGUE	-	-	-	1	2	1
	FEVER	3	5	3	4	6	4
	MULTIPLE ORGAN FAILURE	1	2	1	-	-	-
	OEDEMA PERIPHERAL	-	-	-	1	2	1
	SYNCOPE	-	-	-	1	2	1
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL	1	2	1	-	-	-
	BLOOD PRESSURE FLUCTUATION	1	2	1	-	-	-
GASTRO-INTESTINAL SYSTEM DISORDERS	TOTAL	3	5	3	4	6	4
	DUODENAL ULCER	1	2	1	-	-	-
	DUODENAL ULCER HAEMORRHAGIC	-	-	-	1	2	1
	GASTRITIS HAEMORRHAGIC	1	2	1	-	-	-
	ILEUS	-	-	-	1	2	1
	NAUSEA	-	-	-	1	2	1
	PEPTIC ULCER HAEMORRHAGIC	-	-	-	1	2	1
	PERITONITIS	1	2	1	-	-	-
HEART RATE AND RHYTHM DISORDERS	TOTAL	1	2	1	1	2	1
	FIBRILLATION ATRIAL	1	2	1	-	-	-
	FIBRILLATION VENTRICULAR	-	-	-	1	2	1
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL	8	14	8	3	5	4
	COMA HEPATIC	-	-	-	1	2	1
	GALL BLADDER DISORDER	4	7	4	2	3	2
	HEPATIC FAILURE	3	5	3	1	2	1

Table 46 continued. Adverse events by System Organ Class. ITT population.

LIVER AND BILIARY SYSTEM DISORDERS	HEPATORENAL SYNDROME	1	2	1	-	-	-
MYO-,ENDO-,PERICARDIAL & VALVE DISORDERS	TOTAL	1	2	1	-	-	-
	MYOCARDIAL INFARCTION	1	2	1	-	-	-
PLATELET, BLEEDING & CLOTTING DISORDERS	TOTAL	1	2	1	2	3	2
	HAEMORRHAGE NOS	1	2	1	-	-	-
	THROMBOSIS	-	-	-	1	2	1
	THROMBOSIS ARTERIAL LEG	-	-	-	1	2	1
PSYCHIATRIC DISORDERS	TOTAL	-	-	-	3	5	4
	ANXIETY	-	-	-	1	2	1
	CONFUSION	-	-	-	1	2	1
	PSYCHOSIS	-	-	-	1	2	1
	SOMNOLENCE	-	-	-	1	2	1
RED BLOOD CELL DISORDERS	TOTAL	1	2	1	1	2	1
	ANAEMIA	1	2	1	1	2	1
REPRODUCTIVE DISORDERS, FEMALE	TOTAL	-	-	-	1	2	1
	OVARIAN CYST	-	-	-	1	2	1
RESISTANCE MECHANISM DISORDERS	TOTAL	6	10	7	6	10	6
	ABSCESS	4	7	5	3	5	3
	HERPES ZOSTER	-	-	-	1	2	1
	INFECTION	-	-	-	1	2	1
	MONILIASIS	1	2	1	-	-	-
	SEPSIS	1	2	1	1	2	1
RESPIRATORY SYSTEM DISORDERS	TOTAL	6	10	6	8	13	8
	BRONCHITIS	1	2	1	1	2	1
	DYSPNOEA	1	2	1	-	-	-
	PLEURAL EFFUSION	2	3	2	2	3	2
	PLEURISY	-	-	-	1	2	1

[4] Sponsor comment: Post-operative haemorrhage (TachoSil), anaemia (TachoSil), abscess and pleural effusion (argon beamer).

[5] Sponsor comment: Two events were possible related to TachoSil (post-operative haemorrhage, n=1) and argon beamer (abscess and pleural effusion, n=1). 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). l

		TachoComb S			Argon beamer		
		N=59			N=62		
		n	%	E	n	%	E
RESPIRATORY SYSTEM DISORDERS	PNEUMONIA	2	3	2	4	6	4
SECONDARY TERMS - EVENTS	TOTAL	7	12	7	3	5	3
	POST-OPERATIVE HAEMORRHAGE	3	5	3	1	2	1
	POST-OPERATIVE WOUND INFECTION	4	7	4	2	3	2
SKIN AND APPENDAGES DISORDERS	TOTAL	-	-	-	1	2	1
	FISTULA INCOMPLETE	-	-	-	1	2	1
URINARY SYSTEM DISORDERS	TOTAL	8	14	8	3	5	4
	CYSTITIS	3	5	3	2	3	2
	RENAL FAILURE ACUTE	1	2	1	-	-	-
	RENAL FUNCTION ABNORMAL	2	3	2	-	-	-
	URINARY TRACT INFECTION	2	3	2	1	2	2
WHITE CELL AND RES DISORDERS	TOTAL	1	2	1	-	-	-
	LEUKOCYTOSIS	1	2	1	-	-	-

N = Number of exposed, n = Number with event, % = Number with event as % of exposed
E = Number of events

Table 47. Adverse events by severity and causality. ITT population.

Number of Events	ADVERSE EVENTS BY SEVERITY AND CAUSALITY							
	TachoComb S				Argon beamer			
	Mild	Moderate	Severe	All	Mild	Moderate	Severe	All
RELATION TO DRUG								
Possible	-	2	-	2	-	2	-	2
Unlikely	6	3	3	12	2	6	-	8
Not related	8	12	14	34	18	15	4	37
Not assessable	1	1	-	2	-	-	-	-
All	15	18	17	50	20	23	4	47

Table 48. Serious adverse events by System Organ Class. ITT population.

		TachoComb S			Argon beamer		
		N=59			N=62		
		n	%	E	n	%	E
TOTAL	TOTAL	14	24	23	7	11	14
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL	1	2	1	-	-	-
	MULTIPLE ORGAN FAILURE	1	2	1	-	-	-
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL	1	2	1	-	-	-
	BLOOD PRESSURE FLUCTUATION	1	2	1	-	-	-
GASTRO-INTESTINAL SYSTEM DISORDERS	TOTAL	1	2	1	2	3	2
	ILEUS	-	-	-	1	2	1
	PEPTIC ULCER HAEMORRHAGIC	-	-	-	1	2	1
	PERITONITIS	1	2	1	-	-	-
HEART RATE AND RHYTHM DISORDERS	TOTAL	1	2	1	-	-	-
	FIBRILLATION ATRIAL	1	2	1	-	-	-
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL	6	10	6	2	3	3
	COMA HEPATIC	-	-	-	1	2	1
	GALL BLADDER DISORDER	2	3	2	1	2	1
	HEPATIC FAILURE	3	5	3	1	2	1
	HEPATORENAL SYNDROME	1	2	1	-	-	-
MYO-,ENDO-,PERICARDIAL & VALVE DISORDERS	TOTAL	1	2	1	-	-	-
	MYOCARDIAL INFARCTION	1	2	1	-	-	-
PLATELET, BLEEDING & CLOTTING DISORDERS	TOTAL	1	2	1	2	3	2
	HAEMORRHAGE NOS	1	2	1	-	-	-
	THROMBOSIS	-	-	-	1	2	1
	THROMBOSIS ARTERIAL LEG	-	-	-	1	2	1
PSYCHIATRIC DISORDERS	TOTAL	-	-	-	1	2	1
	PSYCHOSIS	-	-	-	1	2	1
RESISTANCE MECHANISM DISORDERS	TOTAL	3	5	3	4	6	4
	ABSCESS	2	3	2	3	5	3
	SEPSIS	1	2	1	1	2	1

(Continued)

N = Number of exposed, n = Number with event, % = Number with event as % of exposed
E = Number of events

		TachoComb S			Argon beamer		
		N=59			N=62		
		n	%	E	n	%	E
RESPIRATORY SYSTEM DISORDERS	TOTAL	2	3	2	1	2	1
	DYSPNOEA	1	2	1	-	-	-
	PLEURAL EFFUSION	-	-	-	1	2	1
	PNEUMONIA	1	2	1	-	-	-
SECONDARY TERMS - EVENTS	TOTAL	3	5	3	-	-	-
	POST-OPERATIVE HAEMORRHAGE	2	3	2	-	-	-
	POST-OPERATIVE WOUND INFECTION	1	2	1	-	-	-
SKIN AND APPENDAGES DISORDERS	TOTAL	-	-	-	1	2	1
	FISTULA INCOMPLETE	-	-	-	1	2	1
URINARY SYSTEM DISORDERS	TOTAL	3	5	3	-	-	-
	RENAL FAILURE ACUTE	1	2	1	-	-	-
	RENAL FUNCTION ABNORMAL	2	3	2	-	-	-

No significant safety issues were identified.

TC-015-IN

Safety data collected in this study are summarised below.

In total, 80 (43%) of the patients experienced 163 adverse events during the trial. The numbers of patients reporting at least one adverse event in each treatment group were as follows: 43 (47%) in the TachoSil group and 37 (40%) in the standard treatment group. The most frequent adverse events were constipation, diarrhea, nausea, pyrexia, postoperative fever, pain, insomnia, extravasation of urine and hypertension. Fever and extravasation of urine developed more frequently in the TachoComb S subjects. A total of 13 patients experienced SAEs: 11 events in 9 TachoComb S subjects and 5 events in 4 standard treatment subjects.[6]

Table 49. All adverse events.

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
All	All	43	46.7	99	37	39.8	64
Blood and lymphatic system disorders	All	-	-	-	2	2.2	2
	Leukocytosis	-	-	-	2	2.2	2
Cardiac disorders	All	4	4.3	4	3	3.2	3
	Arrhythmia	1	1.1	1	-	-	-
	Cardiac disorder	1	1.1	1	-	-	-
	Myocardial infarction	1	1.1	1	-	-	-
	Tachyarrhythmia	1	1.1	1	1	1.1	1
	Atrial fibrillation	-	-	-	1	1.1	1
	Cardiac fibrillation	-	-	-	1	1.1	1
Gastrointestinal disorders	All	13	14.1	17	7	7.5	8
	Constipation	6	6.5	6	2	2.2	2
	Diarrhoea	3	3.3	4	1	1.1	1
	Nausea	3	3.3	3	3	3.2	3
	Abdominal pain	1	1.1	1	-	-	-
	Flatulence	1	1.1	1	-	-	-
	Ileus paralytic	1	1.1	1	-	-	-
	Vomiting	1	1.1	1	-	-	-
	Ileus	-	-	-	1	1.1	1
	Subileus	-	-	-	1	1.1	1
General disorders and administration site conditions	All	12	13.0	15	7	7.5	10
	Pyrexia	11	12.0	12	7	7.5	7
	Pain	2	2.2	2	3	3.2	3
	Swelling	1	1.1	1	-	-	-
Immune system disorders	All	-	-	-	2	2.2	2
	Drug hypersensitivity	-	-	-	1	1.1	1

Continued next page.

[6] Sponsor comment: One severe SAE was considered related to trial treatment in a standard treatment subject. No deaths were reported during the trial.

Table 49 continued. All adverse events.

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
Immune system disorders	Iodine allergy	-	-	-	1	1.1	1
Infections and infestations	All	3	3.3	3	5	5.4	5
	Erysipelas	1	1.1	1	-	-	-
	Infection	1	1.1	1	1	1.1	1
	Pneumonia	1	1.1	1	1	1.1	1
	Bronchitis	-	-	-	1	1.1	1
	Postoperative infection	-	-	-	1	1.1	1
	Urinary tract infection	-	-	-	1	1.1	1
Injury, poisoning and procedural complications	All	12	13.0	13	8	8.6	8
	Postoperative fever	4	4.3	4	-	-	-
	Post procedural haemorrhage	2	2.2	2	2	2.2	2
	Post procedural pain	2	2.2	2	2	2.2	2
	Device failure	1	1.1	1	-	-	-
	Foot fracture	1	1.1	1	-	-	-
	Perirenal haematoma	1	1.1	1	-	-	-
	Renal haematoma	1	1.1	1	1	1.1	1
	Wound complication	1	1.1	1	-	-	-
	Anaemia postoperative	-	-	-	1	1.1	1
	Blister	-	-	-	1	1.1	1
	Wound dehiscence	-	-	-	1	1.1	1
Investigations	All	3	3.3	3	-	-	-
	Body temperature increased	2	2.2	2	-	-	-
	Blood potassium decreased	1	1.1	1	-	-	-
Metabolism and nutrition disorders	All	3	3.3	3	1	1.1	1
	Hyperuricaemia	1	1.1	1	-	-	-
	Hypervolaemia	1	1.1	1	-	-	-

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
Metabolism and nutrition disorders	Hypocalcaemia	1	1.1	1	-	-	-
	Hypovolaemia	-	-	-	1	1.1	1
Musculoskeletal and connective tissue disorders	All	3	3.3	4	1	1.1	1
	Arthralgia	1	1.1	1	-	-	-
	Back pain	1	1.1	1	-	-	-
	Flank pain	1	1.1	1	-	-	-
	Gouty arthritis	1	1.1	1	-	-	-
	Fistula	-	-	-	1	1.1	1
Neoplasms benign, malignant and unspecified	All	2	2.2	2	3	3.2	3
(incl cysts and polyps)	Renal cell carcinoma stage unspecified	2	2.2	2	-	-	-
	Lymphoma	-	-	-	1	1.1	1
	Neoplasm progression	-	-	-	1	1.1	1
	Thyroid gland cancer	-	-	-	1	1.1	1
Nervous system disorders	All	1	1.1	1	2	2.2	3
	Syncope	1	1.1	1	1	1.1	1
	Headache	-	-	-	1	1.1	1
	Hyperaesthesia	-	-	-	1	1.1	1
Psychiatric disorders	All	7	7.6	9	6	6.5	6
	Insomnia	4	4.3	4	3	3.2	3
	Sleep disorder	2	2.2	2	-	-	-
	Nervousness	1	1.1	1	-	-	-
	Nicotine dependence	1	1.1	1	-	-	-
	Restlessness	1	1.1	1	-	-	-
	Agitation	-	-	-	1	1.1	1
	Confusional state	-	-	-	1	1.1	1
	Delirium	-	-	-	1	1.1	1

(Continued)

N = Number of exposed, n = Number with event, % = Number with event as % of exposed, E = Number of events

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
Renal and urinary disorders	All	6	6.5	7	2	2.2	2
	Extravasation of urine	3	3.3	3	-	-	-
	Haematuria	-	-	-	2	2.2	2
	Bladder spasm	1	1.1	1	-	-	-
	Urethral obstruction	1	1.1	1	-	-	-
	Urinary bladder haemorrhage	1	1.1	1	-	-	-
	Urinary retention	1	1.1	1	-	-	-
Respiratory, thoracic and mediastinal disorders	All	9	9.8	11	5	5.4	6
	Pneumothorax	2	2.2	2	-	-	-
	Respiratory failure	2	2.2	2	-	-	-
	Cough	1	1.1	2	2	2.2	2
	Aspiration	1	1.1	1	-	-	-
	Asthma	1	1.1	1	-	-	-
	Dyspnoea	1	1.1	1	1	1.1	1
	Pleural effusion	1	1.1	1	1	1.1	1
	Productive cough	1	1.1	1	1	1.1	1
	Pharyngolaryngeal pain	-	-	-	1	1.1	1
Skin and subcutaneous tissue disorders	All	1	1.1	1	-	-	-
	Pruritus	1	1.1	1	-	-	-
Surgical and medical procedures	All	-	-	-	1	1.1	1
	Tumour excision	-	-	-	1	1.1	1
Vascular disorders	All	6	6.5	6	3	3.2	3
	Hypertension	4	4.3	4	2	2.2	2
	Arteriovenous fistula, acquired	1	1.1	1	-	-	-
	Orthostatic hypotension	1	1.1	1	-	-	-
	Wound haemorrhage	-	-	-	1	1.1	1

Table 50. In the text summary of most frequent adverse events (>3%).

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
Gastrointestinal disorders	Constipation	6	6.5	6	2	2.2	2
	Diarrhoea	3	3.3	4	1	1.1	1
	Nausea	3	3.3	3	3	3.2	3
General disorders and administration site conditions	Pyrexia	11	12.0	12	7	7.5	7
	Pain	2	2.2	2	3	3.2	3
Injury, poisoning and procedural complications	Postoperative fever	4	4.3	4	-	-	-
Psychiatric disorders	Insomnia	4	4.3	4	3	3.2	3
Renal and urinary disorders	Extravasation of urine	3	3.3	3	-	-	-
Vascular disorders	Hypertension	4	4.3	4	2	2.2	2

Table 51. All serious adverse events.

		TachoComb S			Standard		
		N= 92			N= 93		
		n	%	E	n	%	E
System Organ Class	Preferred Term						
All	All	9	9.8	11	4	4.3	5
Cardiac disorders	All	2	2.2	2	-	-	-
	Arrhythmia	1	1.1	1	-	-	-
	Myocardial infarction	1	1.1	1	-	-	-
Gastrointestinal disorders	All	2	2.2	2	2	2.2	2
	Diarrhoea	1	1.1	1	1	1.1	1
	Ileus paralytic	1	1.1	1	-	-	-
	Subileus	-	-	-	1	1.1	1
Injury, poisoning and procedural complications	All	1	1.1	1	-	-	-
	Perirenal haematoma	1	1.1	1	-	-	-
Musculoskeletal and connective tissue disorders	All	-	-	-	1	1.1	1
	Fistula	-	-	-	1	1.1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	All	-	-	-	2	2.2	2
	Lymphoma	-	-	-	1	1.1	1
	Thyroid gland cancer	-	-	-	1	1.1	1
Nervous system disorders	All	1	1.1	1	-	-	-
	Syncope	1	1.1	1	-	-	-
Renal and urinary disorders	All	2	2.2	2	-	-	-
	Extravasation of urine	2	2.2	2	-	-	-
Respiratory, thoracic and mediastinal disorders	All	2	2.2	2	-	-	-
	Respiratory failure	2	2.2	2	-	-	-
Vascular disorders	All	1	1.1	1	-	-	-
	Arteriovenous fistula, acquired	1	1.1	1	-	-	-

No significant safety or tolerability issues were noted.

TC-016-IN

Safety data collected in this study are summarised below.

Adverse events were reported for 25/60 (42%) of the TachoSil patients and 28/59 (48%) patients in the argon beamer group. The most frequently reported adverse events were urinary tract infection, myocardial infarction, ascites, wound infection, pneumonia, pleural effusion and pulmonary failure. Of the 92 adverse events reported, none were reported probable and four (n=2/group) 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 treatment emergent adverse events were observed in 10/60 (17%) TachoSil patients and 14/59 (24%) argon beamer subjects.

Six subjects died during the trial; two TachoSil and four argon beamer subjects. [7]

Table 52. Overview of Adverse events.

Population: Safety

		TachoComb S			Argon beamer		
		n	%	E	n	%	E
Number of patients		60	-	-	59	-	-
Number of patients with at least one adverse event (AE)		25	41.7	47	28	47.5	45
Number of patients with at least one treatment emergent AE		25	41.7	47	28	47.5	45
Relationship of treatment emergent AE	Possible	2	3.3	2	2	3.4	2
	Unlikely	24	40.0	45	27	45.8	43
Severity of treatment emergent AE	Mild	12	20.0	15	16	27.1	19
	Moderate	14	23.3	22	10	16.9	18
	Severe	6	10.0	10	6	10.2	8
Serious treatment emergent AE	No	19	31.7	33	18	30.5	30
	Yes	10	16.7	14	14	23.7	15
Withdrawals due to treatment emergent AEs		0	0.0	0	1	1.7	1
Deaths due to treatment emergent AE		2	3.3	3	4	6.8	5

Table 53. Treatment emergent adverse events occurring in more than 1% of the patients.

Population: Safety

SOC / HLT / LLT	TachoComb S			Argon beamer			Total
	n	%	E	n	%	E	(E)
Number of patients	60	-	-	59	-	-	-
Number of patients with a treatment emergent AE	25	41.7	47	28	47.5	45	92
Number of patients with a treatment emergent AE occurring in more than 1% of patients	18	30.0	21	12	20.3	12	33
Cardiac disorders	4	6.7	5	0	0.0	0	5
Ischaemic coronary artery disorders	4	6.7	5	0	0.0	0	5
Myocardial infarction	4	6.7	5	0	0.0	0	5
Gastrointestinal disorders	2	3.3	2	1	1.7	1	3
Abdominal findings abnormal	2	3.3	2	1	1.7	1	3
Ascites	2	3.3	2	1	1.7	1	3
Hepatobiliary disorders	0	0.0	0	2	3.4	2	2
Hepatic failure and associated disorders	0	0.0	0	2	3.4	2	2
Liver failure	0	0.0	0	2	3.4	2	2
Infections and infestations	6	10.0	7	8	13.6	8	15
Infections not elsewhere classified	1	1.7	1	4	6.8	4	5
Wound infection	1	1.7	1	2	3.4	2	3
Infection	0	0.0	0	2	3.4	2	2
Liver and spleen infections	1	1.7	1	1	1.7	1	2

[7] Sponsor comment: No death was considered treatment related.

SOC / HLT / LLT	TachoComb S n	%	E	Argon beamer n	%	E	Total (E)
Liver abscess	1	1.7	1	1	1.7	1	2
Lower respiratory tract and lung infections	3	5.0	3	0	0.0	0	3
Pneumonia	3	5.0	3	0	0.0	0	3
Urinary tract infections	2	3.3	2	3	5.1	3	5
Urinary tract infection	2	3.3	2	1	1.7	1	3
Urinary infection	0	0.0	0	2	3.4	2	2
Renal and urinary disorders	1	1.7	1	1	1.7	1	2
Renal failure and impairment	1	1.7	1	1	1.7	1	2
Oliguria	1	1.7	1	1	1.7	1	2
Respiratory, thoracic and mediastinal disorders	6	10.0	6	0	0.0	0	6
Pneumothorax and pleural effusions not elsewhere classified	3	5.0	3	0	0.0	0	3
Pleural effusion	3	5.0	3	0	0.0	0	3
Respiratory failures (excluding neonatal)	3	5.0	3	0	0.0	0	3
Pulmonary failure	3	5.0	3	0	0.0	0	3

Table 54. Serious Treatment Emergent Adverse Events where causality is Possibly/Possibly

Population: Safety

SOC / HLT / LLT	TachoComb S n	%	E	Argon beamer n	%	E	Total (E)
Number of patients	60	-	-	59	-	-	-
Number of patients with a serious treatment emergent AE where causality is probably/possibly	2	3.3	2	1	1.7	1	3
Gastrointestinal disorders	0	0.0	0	1	1.7	1	1
Gastrointestinal disorders not elsewhere classified	0	0.0	0	1	1.7	1	1
Intra-abdominal haematoma	0	0.0	0	1	1.7	1	1
Infections and infestations	2	3.3	2	0	0.0	0	2
Infections not elsewhere classified	1	1.7	1	0	0.0	0	1
Postoperative abscess	1	1.7	1	0	0.0	0	1
Liver and spleen infections	1	1.7	1	0	0.0	0	1
Liver abscess	1	1.7	1	0	0.0	0	1

Table 55. Treatment Emergent Adverse Events leading to death.

Population: Safety

SOC / HLT / LLT	TachoComb S n	%	E	Argon beamer n	%	E	Total (E)
Number of patients	60	-	-	59	-	-	-
Number of patients with a treatment emergent AE leading to death	2	3.3	3	4	6.8	5	8
Cardiac disorders	2	3.3	3	0	0.0	0	3
Ischaemic coronary artery disorders	2	3.3	3	0	0.0	0	3
Myocardial infarction	2	3.3	3	0	0.0	0	3
Gastrointestinal disorders	0	0.0	0	1	1.7	1	1
Acute and chronic pancreatitis	0	0.0	0	1	1.7	1	1
Pancreatitis necrotising	0	0.0	0	1	1.7	1	1
General disorders and administration site conditions	0	0.0	0	1	1.7	1	1
General signs and symptoms not elsewhere classified	0	0.0	0	1	1.7	1	1
Multiorgan failure	0	0.0	0	1	1.7	1	1
Hepatobiliary disorders	0	0.0	0	2	3.4	2	2
Hepatic failure and associated disorders	0	0.0	0	2	3.4	2	2
Liver failure	0	0.0	0	2	3.4	2	2
Infections and infestations	0	0.0	0	1	1.7	1	1
Sepsis, bacteraemia and viraemia	0	0.0	0	1	1.7	1	1
Septic shock	0	0.0	0	1	1.7	1	1

No significant safety issues were noted.

TC-021 IM

Safety data collected in this study are shown in two tables below; AEs with an incidence >1% by System Organ Class (SOC) (Table 56) and SAEs by causality and SOC (Table 57).[8]

Four subjects died: three TachoSil subjects (due to candida sepsis plus atelectasis; cerebrovascular accident (this subject died approx. 1 month after the 1-month follow-up); pneumonia aspiration plus bronchial fistula) and one standard treatment subject (due to bronchopleural fistula).

Table 56. Adverse events with Incidence >1% by System Organ Class. AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Blood and lymphatic system disorders	TOTAL	4	3	4	5	3	5	9	3	9
	Anaemia	4	3	4	5	3	5	9	3	9
Cardiac disorders	TOTAL	12	8	12	9	6	9	21	7	21
	Atrial fibrillation	11	7	11	5	3	5	16	5	16
	Tachyarrhythmia	1	1	1	4	3	4	5	2	5
Gastrointestinal disorders	TOTAL	9	6	12	10	7	18	19	6	30
	Constipation	5	3	5	9	6	9	14	5	14
	Diarrhoea	1	1	1	2	1	2	3	1	3
	Flatulence	2	1	2	7	5	7	9	3	9
	Nausea	3	2	4	-	-	-	3	1	4
General disorders and administration site conditions	TOTAL	7	5	8	4	3	4	11	4	12
	Pain	2	1	2	1	1	1	3	1	3
	Pyrexia	6	4	6	3	2	3	9	3	9
Infections and infestations	TOTAL	10	7	12	10	7	11	20	7	23
	Cystitis	2	1	2	1	1	1	3	1	3
	Pneumonia	8	5	10	9	6	10	17	6	20
Injury, poisoning and procedural complications	TOTAL	5	3	5	4	3	4	9	3	9
	Anaemia postoperative	2	1	2	1	1	1	3	1	3
	Haemothorax	2	1	2	1	1	1	3	1	3
	Post procedural haemorrhage	1	1	1	2	1	2	3	1	3
Nervous system disorders	TOTAL	1	1	1	3	2	3	4	1	4
	Vocal cord paralysis	1	1	1	3	2	3	4	1	4
Psychiatric disorders	TOTAL	2	1	3	3	2	3	5	2	6
	Sleep disorder	2	1	3	3	2	3	5	2	6
Respiratory, thoracic and mediastinal disorders	TOTAL	23	15	25	28	19	33	51	17	58
	Atelectasis	7	5	7	10	7	10	17	6	17
	Bronchopleural fistula	3	2	4	8	5	10	11	4	14
	Dyspnoea	2	1	2	2	1	2	4	1	4
	Lung disorder	3	2	3	4	3	4	7	2	7

(Continued)

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events
Program:Table_ae_incidence_1percent_AT.sas, Output:Table_ae_incidence_1percent_AT.lst, 02MAR09

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Respiratory, thoracic and mediastinal disorders	Pleural effusion	5	3	5	2	1	2	7	2	7
	Pneumothorax	4	3	4	5	3	5	9	3	9
Vascular disorders	TOTAL	2	1	2	4	3	4	6	2	6
	Hypertension	2	1	2	4	3	4	6	2	6
Skin and subcutaneous tissue disorders	TOTAL	4	3	4	-	-	-	4	1	4
	Pruritus	4	3	4	-	-	-	4	1	4

[8]Sponsor comment: A total of 270 AEs were reported during the trial period; there were 137 events in 66 (44%) TachoSil subjects and 133 events in 66 (44%) standard treatment subjects. Of these events, severity was mild for 198 (91 after TachoSil/107 after standard treatment), moderate for 54 (37/17) and severe for 18 (9/9) of the AEs.
A total of 32 SAEs were reported: 19 events in 16 TachoSil and 13 events in 12 standard treatment subjects. Six events occurred in more than one subject: pneumonia (2 TachoSil/3 standard treatment subjects); pneumothorax (2/1);vocal cord paralysis of laryngeal nerve (1/2); atelectasis (2/0); post-procedural haemorrhage (1/1); bronchopleural fistula (0/2). All deaths were related to the underlying illness or to complications of surgery. In total, two subjects discontinued treatment due to AEs; one patient with candida sepsis and another patient with cerebrovascular accident, both in the TachoSil group.

Table 57. Serious adverse events by causality and System Organ Class. AT

Relationship to trial drug=POSSIBLE

		TachoSil N=149		
		n	%	E
System Organ Class	Preferred Term			
TOTAL	TOTAL	3	2	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	1	1	1
	Drug ineffective	1	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	2	1	2
	Pleural effusion	1	1	1
	Pneumothorax	1	1	1

Table 58. Deaths by System Organ Class. AT

		TachoSil N=149			Standard N=150			Total N=299		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	3	2	5	1	1	1	4	1	6
INFECTIONS AND INFESTATIONS	TOTAL	1	1	1	-	-	-	1	0	1
	Candida sepsis	1	1	1	-	-	-	1	0	1
NERVOUS SYSTEM DISORDERS	TOTAL	1	1	1	-	-	-	1	0	1
	Cerebrovascular accident	1	1	1	-	-	-	1	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	2	1	3	1	1	1	3	1	4
	Atelectasis	1	1	1	-	-	-	1	0	1
	Bronchial fistula	1	1	1	-	-	-	1	0	1
	Bronchopleural fistula	-	-	-	1	1	1	1	0	1
	Pneumonia aspiration	1	1	1	-	-	-	1	0	1

No significant safety issues were noted.

TC-023-IM

Safety data collected in this study are summarised below.

Summaries of AEs with an incidence >1% by SOC and all SAEs (both by SOC) are shown in the tables below.[9, 10]

Four subjects died: two TachoSil subjects (both died due to sepsis with multi-organ failure) and two standard treatment subjects (one due to sepsis with multi-organ failure; one due to ventricular tachycardia, myocardial infarction and respiratory failure).

[9]Sponsor comment: A total of 328 AEs were reported; There were 149 events in 46 (74%) TachoSil subjects and 17 events in 44 (77%) standard treatment subjects. Of these AEs, severity was mild for 135 (70 after TachoSil/65 after standard), moderate for 151 (64/87) and severe for 42 (15/27) of the AEs. One AE was considered possibly related to trial medication: pyrexia after TachoSil, which was non-serious and of mild severity. No AEs were classified as probably related to treatment. A total of 58 SAEs were reported: 15 events in 8 TachoSil subjects and 43 events in 18 standard treatment subjects. Thirteen events occurred in more than one subject: atrial fibrillation (in 1 TachoSil/4 standard treatment subjects); AV block third degree (0/4); multiorgan failure (2/1); wound infection (2/0); cardiac tamponade (1/1); renal failure acute (1/1); tubulointerstitial nephritis (1/1);low cardiac output syndrome (0/2); myocardial infarction (0/2); ventricular tachycardia (0/2); sepsis (0/2); pleural effusion (0/2); pneumothorax (0/2). Of the 58 SAEs, the severity was mild for seven (2/5), moderate for 22 (7/15) and severe for 29 (6/23)

[10] Sponsor comment: No SAEs of this trial were considered possibly or probably related to treatment with TachoSil or standard treatment. No death was considered related to trial treatment. In total, three subjects discontinued treatment due to AEs; two patients in the TachoSil group and one in the standard treatment group (all due to multi-organ failure).

Table 59. Adverse events with incidences >1% by System Organ Class. AT

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Blood and lymphatic system disorders	TOTAL	8	13	12	8	14	11	16	13	23
	Abnormal clotting factor	2	3	2	2	4	2	4	3	4
	Anaemia	3	5	3	1	2	1	4	3	4
	Coagulopathy	1	2	1	1	2	1	2	2	2
	Haemorrhagic anaemia	5	8	5	6	11	6	11	9	11
	Thrombocytopenia	1	2	1	1	2	1	2	2	2
Cardiac disorders	TOTAL	27	44	32	25	44	38	52	44	70
	Atrial fibrillation	18	29	18	14	25	14	32	27	32
	Atrioventricular block third degree	-	-	-	4	7	4	4	3	4
	Bradycardia	1	2	1	3	5	3	4	3	4
	Cardiac tamponade	1	2	2	1	2	1	2	2	3
	Low cardiac output syndrome	2	3	2	2	4	2	4	3	4
	Myocardial infarction	-	-	-	2	4	2	2	2	2
	Pericardial effusion	3	5	3	4	7	4	7	6	7
	Supraventricular tachycardia	-	-	-	2	4	2	2	2	2
	Tachyarrhythmia	4	6	4	4	7	4	8	7	8
	Ventricular tachycardia	-	-	-	2	4	2	2	2	2
	Atrial flutter	2	3	2	-	-	-	2	2	2
Gastrointestinal disorders	TOTAL	12	19	12	8	14	9	20	17	21
	Constipation	3	5	3	3	5	3	6	5	6
	Nausea	8	13	8	5	9	5	13	11	13
	Vomiting	1	2	1	1	2	1	2	2	2
General disorders and administration site conditions	TOTAL	6	10	6	4	7	4	10	8	10
	Multi-organ failure	2	3	2	1	2	1	3	3	3
	Pyrexia	4	6	4	3	5	3	7	6	7

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Blood and lymphatic system disorders	TOTAL	8	13	12	8	14	11	16	13	23
	Abnormal clotting factor	2	3	2	2	4	2	4	3	4
	Anaemia	3	5	3	1	2	1	4	3	4
	Coagulopathy	1	2	1	1	2	1	2	2	2
	Haemorrhagic anaemia	5	8	5	6	11	6	11	9	11
	Thrombocytopenia	1	2	1	1	2	1	2	2	2
Cardiac disorders	TOTAL	27	44	32	25	44	38	52	44	70
	Atrial fibrillation	18	29	18	14	25	14	32	27	32
	Atrioventricular block third degree	-	-	-	4	7	4	4	3	4
	Bradycardia	1	2	1	3	5	3	4	3	4
	Cardiac tamponade	1	2	2	1	2	1	2	2	3
	Low cardiac output syndrome	2	3	2	2	4	2	4	3	4
	Myocardial infarction	-	-	-	2	4	2	2	2	2
	Pericardial effusion	3	5	3	4	7	4	7	6	7
	Supraventricular tachycardia	-	-	-	2	4	2	2	2	2
	Tachyarrhythmia	4	6	4	4	7	4	8	7	8
	Ventricular tachycardia	-	-	-	2	4	2	2	2	2
	Atrial flutter	2	3	2	-	-	-	2	2	2
Gastrointestinal disorders	TOTAL	12	19	12	8	14	9	20	17	21
	Constipation	3	5	3	3	5	3	6	5	6
	Nausea	8	13	8	5	9	5	13	11	13
	Vomiting	1	2	1	1	2	1	2	2	2
General disorders and administration site conditions	TOTAL	6	10	6	4	7	4	10	8	10
	Multi-organ failure	2	3	2	1	2	1	3	3	3
	Pyrexia	4	6	4	3	5	3	7	6	7

Table continued on the next page.

Table 59 continued. Adverse events with incidences >1% by System Organ Class. AT

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
Renal and urinary disorders	Tubulointerstitial nephritis	1	2	1	1	2	1	2	2	2
Respiratory, thoracic and mediastinal disorders	TOTAL	22	35	25	18	32	24	40	34	49
	Cough	2	3	2	1	2	1	3	3	3
	Dyspnoea	1	2	1	1	2	1	2	2	2
	Pleural effusion	14	23	14	11	19	14	25	21	28
	Pneumothorax	4	6	4	4	7	5	8	7	9
	Respiratory failure	-	-	-	3	5	3	3	3	3
	Asthma	2	3	2	-	-	-	2	2	2
	Pulmonary congestion	2	3	2	-	-	-	2	2	2
Skin and subcutaneous tissue disorders	TOTAL	1	2	1	1	2	1	2	2	2
	Subcutaneous emphysema	1	2	1	1	2	1	2	2	2
Vascular disorders	TOTAL	3	5	3	6	11	6	9	8	9
	Hypertension	1	2	1	1	2	1	2	2	2
	Hypotension	2	3	2	5	9	5	7	6	7

N = number of exposed, n = number with event, % = number with event as % of exposed, E = number of events

Table 60. All Serious Adverse Events by System Organ Class. AT.

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	8	13	15	18	32	43	26	22	58
CARDIAC DISORDERS	TOTAL	2	3	3	10	18	16	12	10	19
	Atrial fibrillation	1	2	1	4	7	4	5	4	5
	Atrioventricular block third degree	-	-	-	4	7	4	4	3	4
	Cardiac arrest	-	-	-	1	2	1	1	1	1
	Cardiac tamponade	1	2	2	1	2	1	2	2	3
	Low cardiac output syndrome	-	-	-	2	4	2	2	2	2
	Myocardial infarction	-	-	-	2	4	2	2	2	2
	Ventricular tachycardia	-	-	-	2	4	2	2	2	2
GASTROINTESTINAL DISORDERS	TOTAL	-	-	-	1	2	1	1	1	1
	Colitis ischaemic	-	-	-	1	2	1	1	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	TOTAL	2	3	2	1	2	1	3	3	3
	Multi-organ failure	2	3	2	1	2	1	3	3	3
INFECTIONS AND INFESTATIONS	TOTAL	4	6	5	4	7	4	8	7	9
	Mediastinitis	1	2	1	-	-	-	1	1	1
	Pneumonia klebsiella	-	-	-	1	2	1	1	1	1
	Postoperative wound infection	-	-	-	1	2	1	1	1	1
	Sepsis	-	-	-	2	4	2	2	2	2
	Staphylococcal bacteraemia	1	2	1	-	-	-	1	1	1
	Wound infection	2	3	2	-	-	-	2	2	2
	Wound infection staphylococcal	1	2	1	-	-	-	1	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	TOTAL	2	3	2	2	4	4	4	3	6
	Brain contusion	-	-	-	1	2	1	1	1	1
	Cardiac function disturbance postoperative	1	2	1	-	-	-	1	1	1
	Haemothorax	-	-	-	1	2	1	1	1	1
	Post procedural haemorrhage	1	2	1	-	-	-	1	1	1
	Post procedural stroke	-	-	-	1	2	1	1	1	1
	Stent-graft endoleak	-	-	-	1	2	1	1	1	1

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
NERVOUS SYSTEM DISORDERS	TOTAL	1	2	1	2	4	2	3	3	3
	Cerebral infarction	1	2	1	-	-	-	1	1	1
	Cerebrovascular accident	-	-	-	1	2	1	1	1	1
	Vocal cord paralysis	-	-	-	1	2	1	1	1	1
PSYCHIATRIC DISORDERS	TOTAL	-	-	-	1	2	1	1	1	1
	Mental disorder due to a general medical condition	-	-	-	1	2	1	1	1	1
RENAL AND URINARY DISORDERS	TOTAL	2	3	2	2	4	2	4	3	4
	Renal failure acute	1	2	1	1	2	1	2	2	2
	Tubulointerstitial nephritis	1	2	1	1	2	1	2	2	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	TOTAL	-	-	-	7	12	10	7	6	10
	Acute respiratory failure	-	-	-	1	2	1	1	1	1
	Pleural effusion	-	-	-	2	4	5	2	2	5
	Pneumothorax	-	-	-	2	4	2	2	2	2
	Pulmonary embolism	-	-	-	1	2	1	1	1	1
	Respiratory failure	-	-	-	1	2	1	1	1	1
VASCULAR DISORDERS	TOTAL	-	-	-	2	4	2	2	2	2
	Haemorrhage	-	-	-	1	2	1	1	1	1
	Hypotension	-	-	-	1	2	1	1	1	1

Table 61. Deaths by System Organ Class. AT

		TachoSil N=62			Standard N=57			Total N=119		
		n	%	E	n	%	E	n	%	E
System Organ Class	Preferred Term									
TOTAL	TOTAL	2	3	2	2	4	4	4	3	6
CARDIAC DISORDERS	TOTAL	-	-	-	1	2	2	1	1	2
	Myocardial infarction	-	-	-	1	2	1	1	1	1
	Ventricular tachycardia	-	-	-	1	2	1	1	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE	TOTAL	2	3	2	1	2	1	3	3	3
CONDITIONS	Multi-organ failure	2	3	2	1	2	1	3	3	3
RESPIRATORY, THORACIC AND MEDIASTINAL	TOTAL	-	-	-	1	2	1	1	1	1
DISORDERS	Respiratory failure	-	-	-	1	2	1	1	1	1

There were no significant safety issues noted.

Patient exposure

A total of 1038 were randomly assigned to trial treatment in the 6 pivotal studies listed above, with 1032 receiving trial treatment. Of these, 521 patients were treated with TachoSil. A further 4063 patients, of whom 3839 received TachoSil, were treated in the 5 studies that were supporting studies.

Adverse events

Of the patients receiving treatment in the 6 pivotal studies, adverse events were experienced by 247 patients (47.4%) in the TachoSil treatment group and 238 patients (46.6%) in the comparator treatment group. Information on AEs is included below.

Table 62. Summary of adverse events. All Trials Pool.

	TachoSil **N = 521** **n (%)**	**Comparator** **N = 511** **n (%)**
At least 1 AE	247 (47.4%)	238 (46.6%)
At least 1 treatment-related AE	36 (6.9%)	37 (7.2%)
At least 1 SAE	67 (12.9%)	61 (11.9%)
At least 1 SAE with a fatal outcome	13 (2.5%)	9 (1.8%)

Abbreviations: AE = adverse event; SAE = serious adverse event.

Table 63. Adverse events by System Organ Class. All Trials Pool.

System Organ Class	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 adverse event	**247 (47.4%)**	**238 (46.6%)**
Respiratory, thoracic, mediastinal disorders	80 (15.4%)	81 (15.9%)
Cardiac disorders	67(12.9%)	52 (10.2%)
Infections and infestations	53 (10.2%)	61 (11.9%)
Gastrointestinal disorders	48 (9.2%)	37 (7.2%)
General disorders and administration site conditions	46 (8.8%)	37 (7.2%)
Injury, poisoning, and procedural complications	34 (6.5%)	26 (5.1%)
Vascular disorders	20 (3.8%)	27 (5.3%)
Renal and urinary disorders	23 (4.4%)	13 (2.5%)
Psychiatric disorders	16 (3.1%)	20 (3.9%)
Nervous system disorders	12 (2.3%)	20 (3.9%)
Blood and lymphatic system disorders	16 (3.1%)	15 (2.9%)
Metabolism and nutrition disorders	17 (3.3%)	14 (2.7%)
Investigations	13 (2.5%)	17 (3.3%)
Skin and subcutaneous tissue disorders	13 (2.5%)	6 (1.2%)
Hepatobiliary disorders	4 (0.8%)	7 (1.4%)
Musculoskeletal and connective tissue disorders	5 (1.0%)	3 (0.6%)
Neoplasms benign, malignant, and unspecified	4 (0.8%)	4 (0.8%)
Immune system disorders	0	6 (1.2%)
Surgical and medical procedures	2 (0.4%)	2 (0.4%)
Eye disorders	2 (0.4%)	0
Ear and labyrinth disorders	1 (0.2%)	0
Endocrine disorders	0	1 (0.2%)

At each level of patient summarisation, a patient is counted once if the patient reported 1 or more events.

Table 64. Adverse events reported in at least 1% of patients in either treatment group. All Trials Pool.

Adverse Event (Preferred Term)	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 adverse event	**247 (47.4%)**	**238 (46.6%)**
Atrial fibrillation	32 (6.1%)	30 (5.9%)
Pyrexia	30 (5.8%)	25 (4.9%)
Pleural effusion	24 (4.6%)	20 (3.9%)
Pneumonia	16 (3.1%)	21 (4.1%)
Nausea	15 (2.9%)	9 (1.8%)
Pneumothorax	14 (2.7%)	20 (3.9%)
Constipation	14 (2.7%)	15 (2.9%)
Tachyarrhythmia	11 (2.1%)	11 (2.2%)
Hypertension	11 (2.1%)	9 (1.8%)
Wound infection	10 (1.9%)	4 (0.8%)
Atelectasis	9 (1.7%)	14 (2.7%)
Post-procedural haemorrhage	9 (1.7%)	9 (1.8%)
Anaemia	8 (1.5%)	7 (1.4%)
Pain	7 (1.3%)	5 (1.0%)
Respiratory failure	7 (1.3%)	4 (0.8%)
Pruritus	7 (1.3%)	0
Hypotension	6 (1.2%)	7 (1.4%)
Hyperglycemia	6 (1.2%)	7 (1.4%)
Sleep disorder	6 (1.2%)	3 (0.6%)
Haemorrhagic anaemia	5 (1.0%)	6 (1.2%)
Cystitis	5 (1.0%)	4 (0.8%)
Dyspnoea	5 (1.0%)	4 (0.8%)
Insomnia	5 (1.0%)	3 (0.6%)
Myocardial infarction	5 (1.0%)	2 (0.4%)
Procedural site reaction	5 (1.0%)	1 (0.2%)
Urinary tract infection	4 (0.8%)	9 (1.8%)
Bronchopleural fistula	3 (0.6%)	8 (1.6%)
Flatulence	3 (0.6%)	8 (1.6%)
Vocal cord paralysis	1 (0.2%)	5 (1.0%)
Haemoglobin decreased	0	5 (1.0%)

At each level of patient summarisation, a patient is counted once if the patient reported 1 or more events.

Table 65. Adverse events reported in at least 2% of patients in either treatment group. Sealing Trials Pool.

Adverse Event (Preferred Term)	TachoSil N = 245 n (%)	Comparator N = 243 n (%)
At least 1 adverse event	**105 (42.9%)**	**108 (44.4%)**
Atrial fibrillation	13 (5.3%)	15 (6.2%)
Pneumonia	10 (4.1%)	15 (6.2%)
Atelectasis	9 (3.7%)	13 (5.3%)
Pyrexia	9 (3.7%)	12 (4.9%)
Pneumothorax	8 (3.3%)	16 (6.6%)
Pleural effusion	6 (2.4%)	6 (2.5%)
Tachyarrhythmia	5 (2.0%)	6 (2.5%)
Constipation	5 (2.0%)	9 (3.7%)
Pruritus	5 (2.0%)	0
Hypertension	4 (1.6%)	6 (2.5%)
Anemia	4 (1.6%)	5 (2.1%)
Bronchopleural fistula	3 (1.2%)	8 (3.3%)
Flatulence	2 (0.8%)	7 (2.9%)

At each level of patient summarisation, a patient is counted once if the patient reported 1 or more events.

Table 66. Adverse events reported in at least 2% of patients in either treatment group. Haemostasis Trials Pool.

Adverse Event (Preferred Term)	TachoSil N = 276 n (%)	Comparator N = 268 n (%)
At least 1 adverse event	**142 (51.4%)**	**130 (48.5%)**
Pyrexia	21 (7.6%)	13 (4.9%)
Atrial fibrillation	19 (6.9%)	15 (5.6%)
Pleural effusion	18 (6.5%)	14 (5.2%)
Nausea	11 (4.0%)	9 (3.4%)
Constipation	9 (3.3%)	6 (2.2%)
Wound infection	9 (3.3%)	3 (1.1%)
Post-procedural haemorrhage	7 (2.5%)	7 (2.6%)
Hypertension	7 (2.5%)	3 (1.1%)
Hyperglycemia	6 (2.2%)	7 (2.6%)
Tachyarrhythmia	6 (2.2%)	5 (1.9%)
Pneumonia	6 (2.2%)	6 (2.2%)
Pneumothorax	6 (2.2%)	4 (1.5%)
Haemorrhagic anaemia	5 (1.8%)	6 (2.2%)

At each level of patient summarisation, a patient is counted once if the patient reported 1 or more events.

Table 67. Summary of adverse events by severity. All Trials Pool.

	TachoSil N = 521	Comparator N = 511
Total number of AEs	**546**	**537**
Mild	290	297
Moderate	186	185
Severe	70	55
Number (%) of patients with at least 1 AE	**247 (47.4%)**	**238 (46.6%)**
Mild	112 (21.5%)	124 (24.3%)
Moderate	90 (17.3%)	81 (15.9%)
Severe	45 (8.6%)	33 (6.5%)

Abbreviation: AE = adverse events.
At each level of patient summarisation, a patient is counted only once for the most severe occurrence if the patient reported 1 or more events.

The majority of AEs were of mild or moderate severity. There were 36 patients in the TachoSil group and 37 patients in the comparator treatment groups who experienced AEs that were considered by the investigator to be related to trial treatment. The only individual AEs reported in more than 5% of patients in either treatment group were atrial fibrillation (32 patients in the TachoSil group and 30 patients in the comparator group) and pyrexia (30 patients in the TachoSil group and 25 patients in the comparator group). The overall pattern of AEs observed was similar in the two treatment groups. When the trials were broken down into haemostasis and lung trials, no significant patterns emerged. The incidence of all thromboembolic events was low and was similar in the TachoSil and comparator treatment groups (1.9% and 2.0%, respectively). Similarly, the incidence of bleeding events was similar in both groups; 7.1% and 9.2%, respectively, for the TachoSil and comparator groups. No immune mediated AEs were reported for either group.

Serious adverse events and deaths

A total of 22 deaths from the six pivotal studies were noted; 13 deaths in the TachoSil group and 9 deaths in the comparator treatment group. Of these deaths, there were 4 deaths in the lung lobectomy studies (3 in the TachoSil group versus 1 in the comparator

group) and 18 deaths in the haemostasis studies (10 deaths in the TachoSil group versus 8 deaths in the comparator group). No deaths were felt to be related to the trial treatment.

With regard to serious adverse events (SAEs), these were reported in 67 patients (12.9%) in the TachoSil group and 61 patients (11.9%) in the comparator treatment group. The most commonly reported SAEs in the TachoSil group were respiratory failure, myocardial infarction and postprocedural haemorrhage. The most commonly reported SAEs in the comparator group were pneumonia, atrial fibrillation, pneumothorax, pleural effusion and third degree atrioventricular block. Information on SAEs is included below.

Table 68. Fatal adverse events. All Trials Pool.

Fatal Adverse Event (Preferred Term)	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 fatal adverse event	**13 (2.5%)**	**9 (1.8%)**
Multi-organ failure	3 (0.6%)	2 (0.4%)
Hepatic failure	1 (0.2%)	2 (0.4%)
Myocardial infarction	2 (0.4%)	1 (0.2%)
Renal failure	2 (0.4%)	0
Renal failure acute	1 (0.2%)	0
Acute myocardial infarction	1 (0.2%)	0
Atrial fibrillation	1 (0.2%)	0
Post-procedural bile leak	1 (0.2%)	0
Acute respiratory distress syndrome	1 (0.2%)	0
Atelectasis	1 (0.2%)	0
Bronchial fistula	1 (0.2%)	0
Peritonitis	1 (0.2%)	0
Pneumonia	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0
Candida sepsis	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Haemodynamic instability	1 (0.2%)	0
Haemorrhagic diathesis	1 (0.2%)	0
Metastasis	1 (0.2%)	0
Cerebrovascular accident	1 (0.2%)	0
Ventricular tachycardia	0	1 (0.2%)
Thrombosis	0	1 (0.2%)
Bronchopleural fistula	0	1 (0.2%)
Respiratory failure	0	1 (0.2%)
Septic shock	0	2 (0.4%)
Pancreatitis acute	0	1 (0.2%)
Arteriovenous fistula	0	1 (0.2%)

Table 69. Summary of serious adverse events by System Organ Class. All Trials Pool.

System Organ Class	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 SAE	**67 (12.9%)**	**61 (11.9%)**
Respiratory, thoracic, and mediastinal disorders	20 (3.8%)	15 (2.9%)
Infections and infestations	16 (3.1%)	17 (3.3%)
Cardiac disorders	12 (2.3%)	12 (2.3%)
Injury, poisoning, and procedural complications	11 (2.1%)	7 (1.4%)
Gastrointestinal disorders	6 (1.2%)	7 (1.4%)
Renal and urinary disorders	6 (1.2%)	4 (0.8%)
Nervous system disorders	4 (0.8%)	6 (1.2%)
Hepatobiliary disorders	3 (0.6%)	4 (0.8%)
General disorders and administration site conditions	4 (0.8%)	2 (0.4%)
Vascular disorders	3 (0.6%)	6 (1.2%)
Neoplasms benign, malignant, and unspecified	2 (0.4%)	3 (0.6%)
Psychiatric disorders	0	2 (0.4%)
Blood and lymphatic system disorders	1 (0.2%)	0

Abbreviation: SAE = serious adverse event.

Table 70. Serious adverse events reported by more than 1 patient. All Trials Pool.

Serious Adverse Event (Preferred Term)	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
Respiratory failure	6 (1.2%)	1 (0.2%)
Myocardial infarction	5 (1.0%)	2 (0.4%)
Post-procedural haemorrhage	4 (0.8%)	2 (0.4%)
Pneumonia	3 (0.6%)	5 (1.0%)
Pneumothorax	3 (0.6%)	4 (0.8%)
Hepatic failure	2 (0.4%)	2 (0.4%)
Multi-organ failure	3 (0.6%)	2 (0.4%)
Wound infection	3 (0.6%)	1 (0.2%)
Atrial fibrillation	2 (0.4%)	5 (1.0%)
Pleural effusion	2 (0.4%)	4 (0.8%)
Post-procedural bile leak	2 (0.4%)	2 (0.4%)
Atelectasis	2 (0.4%)	1 (0.2%)
Renal failure acute	2 (0.4%)	1 (0.2%)
Renal failure	2 (0.4%)	0
Procedural site reaction	2 (0.4%)	0
Vocal cord paralysis	1 (0.2%)	3 (0.6%)
Pulmonary embolism	1 (0.2%)	2 (0.4%)
Abdominal abscess	1 (0.2%)	2 (0.4%)
Sepsis	1 (0.2%)	2 (0.4%)
Biliary abscess	1 (0.2%)	1 (0.2%)
Cardiac arrest	1 (0.2%)	1 (0.2%)
Cardiac tamponade	1 (0.2%)	1 (0.2%)
Tachyarrhythmia	1 (0.2%)	1 (0.2%)
Diarrhoea	1 (0.2%)	1 (0.2%)
Arteriovenous fistula	1 (0.2%)	1 (0.2%)
Cerebral infarction	1 (0.2%)	1 (0.2%)
Cerebrovascular accident	1 (0.2%)	1 (0.2%)
Tubulointerstitial nephritis	1 (0.2%)	1 (0.2%)
Bronchopleural fistula	0	2 (0.4%)
Septic shock	0	2 (0.4%)
Low cardiac output syndrome	0	2 (0.4%)
Haemothorax	0	2 (0.4%)
Ventricular tachycardia	0	2 (0.4%)
Subileus	0	2 (0.4%)
Atrioventricular block third degree	0	4 (0.8%)

Table 71. Summary of serious adverse events by severity. All Trials Pool.

	TachoSil N = 521	Comparator N = 511
Total number of SAEs	**95**	**96**
Mild	11	16
Moderate	29	35
Severe	55	45
Number (%) of patients with at least 1 SAE	**67 (12.9%)**	**61 (11.9%)**
Mild	9 (1.7%)	13 (2.5%)
Moderate	19 (3.6%)	19 (3.7%)
Severe	39 (7.5%)	29 (5.7%)

Abbreviation: SAE = serious adverse event.

Table 72. Serious adverse events experienced by more than 1 patient in either treatment group. Sealing Trials Pool.

Serious Adverse Event (Preferred Term)	TachoSil N = 245 n (%)	Comparator N = 243 n (%)
Pneumothorax	3 (1.2%)	2 (0.8%)
Pneumonia	2 (0.8%)	5 (2.1%)
Atelectasis	2 (0.8%)	0
Procedural site reaction	2 (0.8%)	0
Vocal cord paralysis	1 (0.4%)	2 (0.8%)
Bronchopleural fistula	0	2 (0.8%)

Table 73. Serious adverse events experienced by more than 1 patient in either treatment group. Haemostasis Trials Pool.

Serious Adverse Event (Preferred Term)	TachoSil N = 276 n (%)	Comparator N = 268 n (%)
Myocardial infarction	5 (1.8%)	2 (0.7%)
Respiratory failure	5 (1.8%)	1 (0.4%)
Post-procedural haemorrhage	3 (1.1%)	1 (0.4%)
Multi-organ failure	3 (1.1%)	2 (0.7%)
Hepatic failure	2 (0.7%)	2 (0.7%)
Wound infection	3 (1.1%)	1 (0.4%)
Atrial fibrillation	2 (0.7%)	4 (1.5%)
Post-procedural bile leak	2 (0.7%)	2 (0.7%)
Renal failure acute	2 (0.7%)	1 (0.4%)
Renal failure	2 (0.7%)	0
Pleural effusion	1 (0.4%)	3 (1.1%)
Abdominal abscess	1 (0.4%)	2 (0.7%)
Sepsis	1 (0.4%)	2 (0.7%)
Atrioventricular block third degree	0	4 (1.5%)
Septic shock	0	2 (0.7%)
Low cardiac output syndrome	0	2 (0.7%)
Ventricular tachycardia	0	2 (0.7%)
Pneumothorax	0	2 (0.7%)
Subileus	0	2 (0.7%)

The types of SAEs reported were similar between the treatment groups with the exception of respiratory failure, which occurred more frequently in the TachoSil group. However, no respiratory failure was felt to be related to trial treatment. Nine patients in the TachoSil treatment group and 4 patients in the comparator treatment group experienced SAEs that were felt to be related to trial treatment. The incidence of SAEs was lower in both treatment groups in the lung trials than in the haemostasis trials.

Laboratory findings

Haematology parameters were measured in all 6 pivotal studies, liver function tests were measured in the 2 liver trials and in 1 lung trial and coagulation factor data was available from trials TC-013-IN, TC-014-IN, TC-016-IN, TC-021-IM and TC-023-IM. There were no adverse trends identified with regard to administration of TachoSil and laboratory findings.

Safety in special populations

Limited information on safety in special populations was provided. Study TC-019-IN was a prospective, multicentre, Phase IIIb study of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. While there were no specific safety issues identified, this study was abandoned for a number of reasons and the proposed PI notes that use in children is not recommended. Review of overall safety also

revealed no overall differences in safety or effectiveness of TachoSil in patients older than 65 compared to those aged between 18 and 65 years of age.

Immunological events

As noted above, TC-018-IN was an international, non-interventional, prospective, single cohort study of the use of TachoSil in supportive treatment in surgery for improvement of haemostasis where standard treatments are insufficient. One objective of the study was to collect information on immunologic events occurring within 6 months after exposure to TachoSil . A total of 8 patients (0.3%) experienced at least one immunological event during the study, of which one event was deemed serious and 1 patient had 2 non-serious immunological events related to TachoSil. In addition, an Immunology review was provided that noted that no allergic reactions to TachoSil were reported in 37 published studies on TachoSil .

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Post marketing experience

Information on post marketing experience was provided in the application.. Since TachoSil was first registered in 2004, 44 adverse drug reactions were spontaneously reported for 35 patients (figures to 30 June 2009). A total of 38 reactions were considered to be serious and 6 were non-serious. These reactions included 3 cases of Hepatitis C virus (HCV), although no causal relationship could be identified. No new safety concerns have been raised.

Evaluator's overall conclusions on clinical safety

Information on clinical safety was available from the six pivotal studies, as well as a specific study designed to assess safety, TC-018-IN. In addition, information on safety was available from post marketing surveillance.

Information on adverse events was collected from all pivotal studies. Adverse events (AEs) were experienced by 247 patients (47.4%) in the TachoSil treatment group and 238 patients (46.6%) in the comparator treatment group. Given the nature of the underlying conditions and surgery, this was not unexpected (lung/ liver resection). The majority of AEs were of mild or moderate severity. The only individual AEs reported in more than 5% of patients in either treatment group were atrial fibrillation and pyrexia. The overall pattern of AEs observed was similar in the two treatment groups. The incidence of all thromboembolic events was low and was similar in the TachoSil and comparator treatment groups. Similarly the incidence of bleeding events was similar in both groups. No immune mediated AEs were reported for either group.

A total of 22 deaths from the six pivotal studies were noted, with 13 deaths in the TachoSil group and 9 deaths in the comparator treatment group. Once again, given the serious nature of many of the underling conditions, including malignancy, this was not unexpected. No deaths were felt to be related to the trial treatment. Serious adverse events were reported in 67 patients (12.9%) in the TachoSil group and 61 patients (11.9%) in the comparator treatment group. The most commonly reported SAEs in the TachoSil group were respiratory failure, myocardial infarction and postprocedural

haemorrhage. The most commonly reported SAEs in the comparator group were pneumonia, atrial fibrillation, pneumothorax, pleural effusion and third degree atrioventricular block.

No specific safety issues were identified in terms of laboratory findings, special populations or immunological events.

The specific safety study, *TC-018-IN,* was designed to collect information on thromboembolic events, immunologic events and drug interactions leading to thromboembolic events or major bleeding occurring within 6 months after exposure to TachoSil. The primary endpoint was the proportion of patients experiencing a thromboembolic event verified by paraclinical examination. A total of 46 patients (1.5%) experienced at least one thromboembolic event, of which 41 patients had a serious thromboembolic event and 2 patients had a serious thromboembolic event related to TachoSil . No specific safety issues were identified.

Information from post marketing surveillance was also provided. Since TachoSil was first registered in 2004, 44 adverse drug reactions were spontaneously reported for 35 patients (figures to 30 June 2009). No significant safety issues have been identified.

Clinical summary and conclusions

Clinical aspects

Pharmacokinetics

TachoSil is intended for topical application only. Intravascular pharmacokinetic studies were not performed in humans.

Pharmacodynamics

No pharmacodynamic studies were performed on humans due to ethical issues with testing on normal humans as well as the fact that the active constituents, human fibrinogen and human thrombin are well established in clinical use.

Clinical efficacy

Dose-response studies and main clinical studies

No dose response studies were performed on humans. Information on clinical efficacy was provided by 6 pivotal studies, TC-013-IN, TC-014-IN, TC-015-IN, TC-016-IN, TC-021-IM and TC-023-IM. Of these, four studies (TC-014-IN, TC-015-IN, TC-016-IN and TC-023-IM) were designed to evaluate the haemostatic efficacy and safety of TachoSil in three different surgical applications. These were open-label, multi-centre, randomised, controlled, parallel-group studies that compared TachoSil with surgical standard treatment. Comparator treatments used in these trials were argon beam coagulator, standard surgical techniques (additional suturing) or haemostatic fleece material without additional active coagulation-stimulating compounds. The different surgical applications were liver resection (TC-014-IN and TC-016-IN), kidney resection (TC-015-IN) and cardiovascular surgery (TC-021-IM). Two pivotal studies (TC-013-IN and TC-021-IM) were designed to evaluate efficacy in tissue sealing following lung lobectomy surgery. These were randomised, open, parallel-group, multi-centre trials comparing the intra- and postoperative effect of TachoSil treatment versus standard surgical treatment as secondary treatment of air leakage in patients undergoing lung lobectomy.

These studies were adequately designed and powered, and met the requirements of the TGA adopted EU Guidance document "Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/ Haemostatic Products[1]. In particular, clinical endpoints appeared to be appropriate and have clinical significance. All four haemostatic efficacy studies

demonstrated a significant difference in favour of TachoSil for the primary efficacy endpoint. For the two sealing efficacy studies, no significant difference in favour of TachoSil was demonstrated, although results favoured TachoSil over the comparator.

Clinical studies in special populations

One study, *TC-019-IN*, was designed to assess efficacy of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. Unfortunately this study was abandoned prematurely for reasons unrelated to the product and little useful information could be gained. An indication for paediatric use is not being sought.

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis was performed for both the haemostatic efficacy and sealing efficacy of TachoSil. While both pooled analyses favoured TachoSil over comparator, interpretation was complicated by the different surgery types, different comparators and different primary efficacy endpoints.

Supportive studies

Further information on efficacy was provided by three uncontrolled studies (TS-001-WE, TC-022-IT and TC-027-DE) and three ongoing studies (TC-026-JP, TC-029-IM and TC-031-DE). Minimal information on these studies was provided.

Clinical safety

Patient exposure

A total of 1038 patients were randomly assigned to trial treatment in the 6 pivotal studies, with 1032 receiving trial treatment. Of these, 521 patients were treated with TachoSil . A further 4063 patients, of whom 3839 received TachoSil, were treated in the 5 studies that were supporting studies.

Adverse events

Information on adverse events was collected from all pivotal studies. Adverse events were experienced by 247 patients (47.4%) in the TachoSil treatment group and 238 patients (46.6%) in the comparator treatment group. Given the nature of the underlying conditions and surgery, this was not unexpected (lung/ liver resection). The majority of AEs were of mild or moderate severity. The only individual AEs reported in more than 5% of patients in either treatment group were atrial fibrillation and pyrexia. The overall pattern of AEs observed was similar in the two treatment groups.

Serious adverse events and deaths

A total of 22 deaths from the six pivotal studies were noted; 13 deaths in the TachoSil group and 9 deaths in the comparator treatment group. Given the serious nature of many of the underlying conditions, including malignancy, this was not unexpected. No deaths were felt to be related to the trial treatment. Serious adverse events were reported in 67 patients (12.9%) in the TachoSil group and 61 patients (11.9%) in the comparator treatment group. The most commonly reported SAEs in the TachoSil group were respiratory failure, myocardial infarction and postprocedural haemorrhage. The most commonly reported SAEs in the comparator group were pneumonia, atrial fibrillation, pneumothorax, pleural effusion and third degree atrioventricular block.

Laboratory findings

There were no significant laboratory findings noted from any of the pivotal studies related to either TachoSil or comparator.

Safety in special populations

There was limited information about safety in special populations. One study, TC-019-IN, was designed to assess efficacy and safety of TachoSil in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation. Unfortunately this study was abandoned prematurely for reasons unrelated to the product and little useful information could be gained, either in terms of safety or efficacy. An indication for paediatric use is not being sought. A review of safety in older patients (>65) receiving TachoSil did not demonstrate any significant differences to the younger (18 to 65) age group.

Immunological events

One study, TC-018-IN was an international, non-interventional, prospective, single cohort study of the use of TachoSil in supportive treatment in surgery for improvement of haemostasis where standard treatments are insufficient. One objective of the study was to collect information on immunologic events occurring within 6 months after exposure to TachoSil . A total of 8 patients (0.3%) experienced at least one immunological event during the study, of which one event was deemed serious, and 1 patient had 2 non-serious immunological events related to TachoSil . In addition, an Immunology review was provided that noted that no allergic reactions to TachoSil were reported in 37 published studies on TachoSil .

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Benefit risk assessment

Benefits

TachoSil is a ready-to-use degradable surgical sponge developed for topical use to support intraoperative haemostasis and tissue sealing. It is intended to be applied directly to a wound surface, where human fibrinogen and human thrombin will be activated. It is particularly envisaged to have application with diffuse capillary oozing as is experienced with liver or renal resection. In this particular scenario, standard surgical techniques such as suturing may be traumatic and cause further damage to the wound surface.

The clinical information provided consisted of 6 pivotal studies, four assessing haemostatic efficacy and two assessing sealing efficacy. The haemostatic efficacy studies demonstrated that TachoSil did appear to result in a reduced time to haemostasis compared to comparators and therefore have significant clinical benefit. The sealing efficacy studies were less conclusive, but results still appeared to favour TachoSil over comparators.

Risks

Any implantable product carries an element of risk, especially in terms of haemorrhage, infection and immune response. Extensive information on safety was provided as part of the application, including safety information from pivotal studies, a specific safety study and post marketing surveillance. As such, risk appears to be acceptable.

Balance

On balance, the IP appears to have a favourable benefit-risk assessment.

Conclusions

TachoSil has a well recognised and documented mechanism of action and has been used overseas extensively since 2004. The information provided indicates that it does have significant utility, particularly in aiding in the control of diffuse capillary oozing. The safety profile has been well established over a number of years and is acceptable. As such, this product has an acceptable benefit-risk assessment.

Recommended conditions for registration

TachoSil is supported for registration in Australia for the following indication;

"TachoSil is indicated as an adjunct to haemostasis and tissue sealing in surgery in adults".

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP Ver 3.0 dated 7 November 2008) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is described in Table 74 below.

Table 74. Ongoing Safety Concerns:

Important identified risks	-Thromboembolic events
Important potential risks	-Immunological events -Transmission of infectious agents -Drug-drug interactions -Atrial fibrillation -Pyrexia -Off-label use (sealing)
Important missing information	-Specific data has not been obtained on the use of TachoSil in neurosurgery or in gastrointestinal anastomosis -The safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials -Repeated use of TachoSil

OPR reviewer comment:

Pursuant to the evaluation of the nonclinical and clinical aspects of the Safety Specifications (SS), the above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities[11] are proposed to monitor all safety concerns. There are no proposed or ongoing clinical trials as part of the proposed pharmacovigilance activities. A Post-authorisation Safety Study (PASS), as part of the requirements by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), has already been conducted and confirmed the established safety profile of TachoSil.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The routine activities that the sponsor has outlined are consistent with the activities outlined in the relevant EU Guidance document[12] and are considered sufficient to monitor the Ongoing Safety Concerns associated with TachoSil.

Risk minimisation activities

Planned actions

As stated in the RMP:

Based on the information already stated in the Product Information and the evaluation of the results from the PASS study confirming the established safety profile of TachoSil, no further risk minimisation activities are considered to be needed at this time to minimise the risk for using TachoSil .

OPR reviewer comment

This was considered acceptable.

In regard to the proposed routine risk minimisation activities, the draft Product Information and Consumer Medicine Information documents are considered satisfactory. In the RMP possible interactions of TachoSil and anticoagulants are discussed and listed as an Important Potential Ongoing Safety Concern (Drug-drug interactions), with the statement "No formal interaction studies have been performed" in the PI. However, there is no mention of possible interactions with TachoSil and the newer direct thrombin inhibitors in the RMP (such as dabigatran). It is recommended that the sponsor update the RMP, including appropriate pharmacovigilance and risk minimisation activities if required, with any available information on drug-drug interactions of TachoSil and direct thrombin inhibitors, such as dabigatran.

Sponsor's conclusion in regard to the need for risk minimisation activities

As stated in the RMP:

As a postauthorisation commitment to the Committee for Medicinal Products for Human Use (CHMP) Nycomed have conducted the PASS study. The background for this study was to confirm the established safety profile of TachoSil with specific focus on thromboembolic events, immunological events, and drug interactions leading to thromboembolic event or major bleeding. Evaluation of the results from the PASS study confirmed the established

[11] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[12] 3.1.2 Routine pharmacovigilance practices. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)

safety profile of TachoSil, and showed no indication that TachoSil causes thromboembolic events, immunological events or major bleeding, neither by itself, nor through drug interactions. Routine risk minimisation activities contained in the current approved Product Information as precautions are described in the table below, and no further risk minimisation activities seem to be needed at this time to minimise the risk for using TachoSil at this time.

The sponsor submitted an updated Risk Management Plan (RMP Version 4.0, dated 9 January 2012), addressing the OPR reviewer's comments above.

OPR reviewer comment

The sponsor's conclusion in regards to routine risk minimisation activities to mitigate the Ongoing Safety Concerns associated with TachoSil is considered acceptable. A PASS has been completed and confirmed the established safety profile of TachoSil. TachoSil has been marketed globally in multiple countries since 2004.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

It is recommended to the Delegate that the sponsor:

1. Submit an updated RMP if this is available or information to assure the TGA that no additional information or significant changes requiring an updated RMP have arisen to the current date. If an updated RMP is available, the sponsor should submit a summary of any differences that exist between these two versions including new Ongoing Safety Concerns and their proposed pharmacovigilance and risk minimisation activities.
2. Update the RMPs language to provide consistency in the Australian context (such as Proposed indication & replace Product Information with PI), or provide an Australian specific annex which identifies these issues and any Australian relevant changes.
3. Update the instructions in the Product Information on the average time or degree a sponge should be pre-moistened in saline solution before application to the patient to avoid medication errors.
4. Update the RMP, including appropriate pharmacovigilance and risk minimisation activities if required, with any available information on drug-drug interactions of TachoSil and direct thrombin inhibitors, such as dabigatran.

The sponsor submitted an updated Risk Management Plan (RMP Version 4.0, dated 9 January 2012), addressing the OPR reviewer's comments above.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The application was considered at the 2011.7 meeting of the Pharmaceutical Subcommittee (PSC) on 21 November 2011. The PSC endorsed the questions raised by the TGA. There were sterility issues to be resolved at the time of writing.

Routine batch release conditions were proposed.

Nonclinical

A fixed combination of 5.5 mg/cm^2 fibrinogen and 2.0 IU/cm^2 thrombin in TachoComb provided the optimal adhesive strength in rat kidney and rat liver wounds. This supports the fixed combination doses of fibrinogen and thrombin in TachoSil for clinical use.

Despite the limitations of animal studies with human proteins, the tolerance of TachoSil at intraperitoneal tissue sites was acceptable and there was no evidence of systemic toxicity. The TachoSil sponge had almost completely dissolved within 24 weeks. The lack of genotoxicity, reproductive toxicity and carcinogenicity studies was acceptable given the nature of the product.

Product information and other issues were satisfactorily addressed in the sponsor's response to the Nonclinical Evaluation on 8 November 2011.

The evaluator supported registration.

Clinical

Pharmacology

There were no human pharmacokinetic or pharmacodynamic studies. The active ingredients, human fibrinogen and human thrombin, are well established in clinical use.

Efficacy

There were six pivotal efficacy studies of TachoSil in second line use, four of haemostasis of persistent bleeding that had not responded to standard surgical methods after various surgeries (TC-014-IN, TC-015-IN, TC-016-IN, TC-023-IM) and two of sealing of intraoperative air leakage that had not responded to primary stapling after lung lobectomy (TC-013-IN, TC-021-IM). All were randomised controlled trials in adults. The trials were open-label. TachoSil was applied once only topically during surgery. The primary endpoint in the haemostasis trials was time to haemostasis. The primary endpoints in the air sealing trials were different, being the incidence of air leakage 48 h after surgery in one trial (TC-013-IN) and the duration of post-operative air leakage in the other trial (TC-021-IM).

There was an uncontrolled trial in children (TC-019-IN). Three other uncontrolled trials were mentioned but no results given.

In the pivotal haemostatic trials, TachoSil significantly reduced the time to haemostasis of persistent bleeding compared with a standard method after liver resection, renal resection and cardiovascular surgery (Table 75). Results for other endpoints were supportive.

In the pivotal air sealing trials after lung lobectomy, TachoSil was not significantly different from a standard method in reducing persistent air leakage 48 h after surgery in one trial (TC-013-IN) and of marginal additional benefit in reducing the duration of persistent air leakage in the other trial (TC-021-IM) (Table 76). The benefit in the second trial was seen in the life table analysis but not the parametric analysis. There results were also reflected in the secondary endpoints. Non-inferiority was not assessed. In the first trial, half the patients did not have air leakage at randomisation which may have influenced the results since these patients may not have required additional treatment.

Table 75. Efficacy in Secondary Haemostasis after Surgery. ITT Population. Time (min)

	TachoSil	Comparator[1]	Difference p-value
Trial TC-014-IN – Liver Resection	***n=59***	***n=62***	
Time to Haemostasis *median (range)*	3 (3-20)	4 (3-39)	p=0.0007[3]
Haemostasis at 10 min *% patients*	97%	90%	p=0.3[2]
Trial TC-016-IN – Liver Resection	**n=60**	**n=59**	
Time to Haemostasis *median (range)*	3 (3-8)	3 (3-23)	p=0.002[4]
Haemostasis at 10 min *% patients*	100%	95%	not stated
Trial TC-015-IN – Kidney Resection	**n=92**	**n=93**	
Time to Haemostasis *median (range)*	3 (3-17)	8 (3-27)	p<0.0001[3]
Haemostasis at 10 min *% patients*	92%	67%	p<0.0001[2]
Trial TC-023-IM - Cardiovascular	**n=59**	**n=60**	
Haemostasis at 3 min *% patients*	75%	33%	p<0.0001[5]
Haemostasis at 6 min *% patients*	95%	72%	p=0.0006[5]

[1] Argon beam coagulator after liver resection, suturing after renal resection and haemostatic fleece after cardiovascular surgery. [2] Fisher's Exact Test. [3] Exploratory parametric analysis. [4]χ^2 Test. [5]Cochran-Mantel-Haenszel Test.

Table 76. Efficacy in Secondary Air Sealing after Lung Lobectomy. ITT Population.

	TachoSil	Standard[1]	Difference p-value
Trial TC-013-IN	**n=96**	**n=93**	
Air Leak Incidence 48h post-surgery %	34%	37%	p=0.76[4]
Intraop Air Leakage Intensity[2] % achieving 1-2 grade reduction	36%	24%	p=0.34[5]
Trial TC-021-IM	**n=148**	**n=151**	
Post-op Duration of Air Leakage[3]			
Life Table Analysis	not stated	not stated	p=0.03[6]
Exploratory Parametric Analysis *median h*	15.3	20.5	p=0.15
Intraop Air Leakage Intensity[2] % achieving 1-2 grade reduction	71%	62%	p=0.042[7]

[1] Sutures in trial TC-013-IN and sutures, staples or no additional treatment in trial TC-021-IM.

[2] Measured intraoperatively under water immersion before randomisation and 3-5 min after application of trial treatment. Grade of air leakage: 0 – none, 1 mild, 2 moderate, 3 severe. 3 This was assessed by cough provocation on the evening after surgery then twice daily until cessation of air leakage. 4 Fisher's Exact Test. 5 Mann-Whitney Test. 6 Log Rank Test. 7 Wilcoxon Signed Rank Sum Test.

The uncontrolled paediatric trial was of the use of TachoSil in secondary haemostasis after liver resection (n=16). Haemostasis was achieved in 14 patients (87.5%). The time to haemostasis was 3-8 min. Because of the limited data, the proposed product information advises against the use of TachoSil in children.

Safety

Safety data from the six pivotal trials and a safety only trial TC-018-IN were presented. In the pivotal trials, 521 patients received a single application of TachoSil and 511 patients received comparator treatment. The pattern of adverse events was similar for TachoSil and the comparator. Common events in both groups were atrial fibrillation, pyrexia, pleural effusion and pneumonia. These events reflect the treated population and the procedure rather than the product itself. There were no deaths deemed related to treatment.

The safety only trial TC-018-IN was an uncontrolled trial of TachoSil as an adjunct to haemostasis in surgery where standard treatments were insufficient. The trial enrolled 3,098 patients. It specifically focussed on thromboembolic and immunological events. The incidence of thromboembolic events was 1.5% (related to TachoSil in 3 patients) and immunological events 0.3% (related to TachoSil in 1 patient).

The evaluator supported registration but recommended limiting the indication to adults because of the limited paediatric data.

Risk management plan

Based on the nonclinical and clinical data, the Safety Specification was considered adequate.

Implementation of the RMP version 3.0 dated 7 November 2008, and subsequent revisions agreed with the Office of Product Review, was recommended as a condition of registration.

Risk-benefit analysis

Delegate considerations

Reports from six pivotal trials were submitted. The development program was consistent with the EU Guideline. TachoSil significantly reduced time to haemostasis when used as an adjunct to standard surgical techniques in haemostasis after liver, renal and cardiovascular surgery. Efficacy was established for this use and could be extrapolated to other surgery except neurosurgery. A specific trial of TachoSil in neurosurgery is required to confirm reliable haemostasis because of the risk that bleeding will compress vital structures.

The TachoSil data for tissue sealing were limited. There were data for air sealing in pulmonary surgery only. The efficacy of TachoSil in this application was not clearly established with marginal benefit in one trial and no difference from standard treatment in the other. Non-inferiority to standard treatment was not assessed. There were no data on the use of TachoSil in gastrointestinal anastomosis or repair of fistulae.

TachoSil was well tolerated with no significant safety concerns except for a small risk of thromboembolic and immunological events. There were no data on repeated use of TachoSil . Repeated use may increase the risk of immunogenicity to the equine collagen component of TachoSil.

The clinical evaluator recommended restricting the indication to adults. The product information advises against use in children (because of limited data) and this is probably sufficient.

TachoSil was used as secondary management of haemostasis after standard surgical techniques in the trials. Therefore, the indication should reflect this with the limitation: "when control of bleeding by standard surgical techniques is ineffective or impractical".

Since efficacy as an adjunct to air sealing or tissue sealing in general was not established, the Delegate did not recommend the product be registered as an adjunct to tissue sealing.

The Delegate has recommended strengthening the **Contraindications** and **Precautions** sections of the product information based on the US product information.

Delegate's draft decision

The Delegate proposed to approve TachoSil Medicated Sponge, containing human fibrinogen and human thrombin, for the indication:

> "*TachoSil is indicated as an adjunct to haemostasis during surgery when control of bleeding by standard surgical techniques is ineffective or impractical".*

Approval will be subject to finalisation of sterility issues and product information.

Proposed conditions of registration:

- Implementation of Batch Release Conditions specified in the Quality and Biopharmaceutics Summary and Request for Advisory Committee on Prescription Medicines (ACPM) Advice and

- Implementation of the Risk Management Plan, version 3.0 dated 7 November 2008, and subsequent revisions as agreed with the Office of Product Review.

The application was submitted to ACPM for advice.

Response from sponsor

Nycomed concurred with the Delegate's proposed action supporting the registration TachoSil for the secondary management of haemostasis when the control of bleeding by standard surgical techniques is ineffective or impractical. Nycomed maintain that the inherent sealant properties of the components which comprise the TachoSil medicated sponge, the nonclinical investigations and clinical data from studies and publications collectively also provide unequivocal support for the sealing properties of TachoSil , and therefore respectfully requested approval of the following indication:

TachoSil is indicated as an adjunct to haemostasis and tissue sealing, when control of bleedingby standard surgical techniques is ineffective or impractical.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview as well as the sponsor's response to these documents, advised the following:

The ACPM agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the indication.

> *TachoSil is indicated as an adjunct to haemostasis during surgery when control of bleeding by standard surgical techniques is ineffective or impractical.*

In making this recommendation, the ACPM considered that the efficacy data from the studies on sealing of intraoperative air leakage that had not responded to primary stapling after lung lobectomy did not support the proposed indication for tissue sealing

The ACPM supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI).

The ACPM endorsed the conditions of registration proposed by the delegate.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of TachoSil medicated sponge blister pack containing human fibrinogen 5.5mg/square cm and human thrombin 2.0IU square cm for the following indication:

> *TachoSil is indicated as an adjunct to haemostasis during surgery when control of bleeding by standard surgical techniques is ineffective or impractical.*

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the human fibrinogen 5.5mg/square cm and human thrombin 2.0IU square cm Risk Management Plan (RMP) version 4.0, dated 9 January 2012, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
2. It is a condition of registration that independent batches of TachoSil Human fibrinogen/Human thrombin human fibrinogen 5.5mg/square cm and human

thrombin 2.0IU/square cm medicated sponge imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

a. Certificates of Analysis of all active ingredient (drug substance) and final product.

b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

c. Evidence of the maintenance of registered storage conditions during transport to Australia.

d. 3 vials/ampoules/cartridges/syringes of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until the sponsor is notified in writing of any variation.

Samples and data should be forwarded to the Biochemistry Section, OLSS at TGA.

Plasma Master File (PMF)

The provision of annual updates for the PMF as per the format outlined in the guideline EMEA/CPMP/BWP/3794/03 "Note for Guidance on the Scientific Data Requirements for a Plasma Master File (PMF)" should be provided as a condition of registration.

Certified Product Details (CPD)

Certified Product Details should be provided as described in the Australian Regulatory Guidelines for Prescription Medicines (Appendix 7).

Shelf-life conditions

The approved shelf-life is for 36 months at ≤25 °C. The sponsor is required to notify the TGA of any out of specification results or trends from the ongoing stability study as they become known, and supply the results upon completion of the study.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION
TACHOSIL® MEDICATED SPONGE

NAME OF THE MEDICINE

The active components of TachoSil medicated sponge are human fibrinogen and human thrombin.

Fibrinogen is a soluble plasma glycoprotein with a molecular weight of approximately 340 kDa, and circulates in plasma as a precursor of fibrin. The native molecule is a homo-dimer, in which both subunits consist of three different polypeptide chains (Aα, Bβ, and γ). All three polypeptide chains of the subunits as well as the dimer are linked with disulfide bonds. Thrombin is a serine protease with a molecular weight of approximately 39 kDa and consists of 295 amino acids. It is formed by two peptide chains of 36 and 259 amino acids respectively, linked by disulfide bonds.

DESCRIPTION

TachoSil is a biodegradable, highly flexible, hygroscopic surgical medicated sponge. The active side of the sponge, which is coated with fibrinogen and thrombin, is marked by a yellow colour. Each TachoSil sponge contains approximately 5.5 mg of human fibrinogen and 2.0 IU of human thrombin per cm^2 as the active ingredients.

Other inactive ingredients include riboflavine, equine collagen, human albumin, sodium chloride, sodium citrate and arginine hydrochloride.

TachoSil is available in three presentations, which differ in the size of the sponge, but not in the composition of the sponge and the coating (see 'Presentation and Storage Conditions').

PHARMACOLOGY

Pharmacodynamics

TachoSil contains fibrinogen and thrombin as a dried coating on the surface of a collagen sponge. Upon contact with physiological fluids such as blood, lymph or physiological saline solution, the components of the coating dissolve and partly diffuse into the wound surface.This is followed by the fibrinogen-thrombin reaction which initiates the last phase of physiological blood coagulation. Fibrinogen is converted into fibrin monomers which spontaneously polymerise into a fibrin clot that adheres the collagen sponge to the wound surface and achieves haemostasis. The fibrin is subsequently cross linked by endogenous factor XIII, creating a firm mechanically stable network with good adhesive properties and therefore provides sealing as well.

Pharmacokinetics

TachoSil is intended for topical application only. Intravascular administration is not possible. As a consequence, intravascular pharmacokinetic studies were not performed in humans.

In animal studies, TachoSil shows progressive biodegradation. The fibrin clot is metabolised in the same way as endogenous fibrin, i.e. by fibrinolysis. The collagen sponge is degraded by phagocytosis and ingrowth of granulation tissue. Approximately 13 weeks after application, only a few remnants were present without any signs of local irritation.

CLINICAL TRIALS

The haemostatic efficacy and safety of TachoSil was evaluated in four open-label, multi-centre, randomised, controlled, parallel-group trials comparing TachoSil with standard surgical treatment in three surgical applications. TachoSil was applied once only topically during surgery. The patients were mostly Caucasian and aged between 18 and 86 years of age.

Liver resection

The data from two trials provide clinical evidence for TachoSil as an adjunct treatment of haemorrhage in patients undergoing at least segmental resection (anatomical or non-anatomical) of the liver. One hundred and twenty-one patients were randomly assigned to either TachoSil (n = 59) or argon beam coagulator treatment (n = 62) in one trial, and 119 patients were treated with either TachoSil (n = 60) or argon beam coagulator (n = 59) in the second trial. Randomisation was conducted intra-operatively if residual minor to moderate (oozing) bleeding was present after primary treatment of major venous or arterial (pulsating) bleeding had been controlled by standard surgical methods. Patient demographics and characteristics, physical condition, past and concomitant illness, concomitant medication, and laboratory tests (haematology, coagulation, liver enzymes) at baseline were similar for the two treatment groups, and the surgical procedures and primary haemostatic treatment were overall well balanced between treatment groups in the two trials.

Both trials demonstrated superiority of TachoSil as secondary haemostatic treatment. The primary efficacy endpoint, time to haemostasis, resulted in a mean (median, range) value of 3.9 (3.0, 3-20) minutes for TachoSil and 6.3 (4.0, 3-39) minutes for argon beamer treated patients, respectively in one trial ($p = 0.0007$), and 3.6 (3.0, 3-8) minutes versus 5.0 (3.0, 3-23) minutes for the TachoSil and the argon beam coagulator treatment group, respectively, in the second liver trial ($p = 0.0018$).

Kidney resection

A trial was conducted to investigate the haemostatic efficacy of TachoSil compared to standard surgery in patients scheduled for the resection of superficial tumours on the kidney. Patient demographics and characteristics, physical condition, past and concomitant illness, concomitant medication, and laboratory tests (haematology and coagulation) at baseline, surgical procedures and primary haemostatic treatment were similar in the two treatment groups. A total of 185 subjects received trial treatment with 92 patients randomised to receive TachoSil and 93 patients to standard treatment. The primary efficacy endpoint was intra-operative time to haemostasis. The results demonstrated that TachoSil was significantly superior to standard surgery. Mean (median, range) time to haemostasis was 5.3 (3.0, 3-17) minutes for TachoSil and 9.5 (8.0, 3-27) minutes for comparator treatment, respectively ($p < 0.0001$).

Cardiovascular surgery

In a cardiovascular trial comparing the efficacy and safety of TachoSil versus standard haemostatic treatment (haemostatic fleece without additional active coagulation stimulating compounds), patients with a planned elective surgery on the heart, the ascending aorta or aortic arch requiring a cardiopulmonary bypass procedure were eligible. Only patients with residual haemorrhage from the heart muscle, the pericardium, a major vessel or vascular bed requiring supportive haemostatic treatment were eligible for randomization. Patient demographics and baseline characteristics including physical condition, past and

concomitant illness, concomitant medication, and laboratory tests were similar for the two treatment groups. In the Intention to Treat (ITT) population, 59 patients were randomised to TachoSil and 60 to standard treatment. The result of the primary efficacy endpoint, proportion of patients with haemostasis at 3 minutes, was 44/59 (75%) for TachoSil treated patients and 20/60 (33%) for standard haemostatic fleece treated patients ($p < 0.0001$).

INDICATIONS

TachoSil is indicated as an adjunct to haemostasis during surgery when control of bleeding by standard surgical techniques is ineffective or impractical.

CONTRAINDICATIONS

Hypersensitivity to the active ingredients or to any of the excipients.

Do not apply TachoSil intravascularly. Intravascular application of TachoSil may result in life-threatening thromboembolic events.

PRECAUTIONS

General

TachoSil is for topical use only. There are no data on repeated application.

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

TachoSil should not be used for the treatment of severe or brisk arterial bleeding because TachoSil has not been evaluated in this treatment.

TachoSil should not be used in procedures involving the renal pelvis or ureter because it may be a focus for calculus formation.

TachoSil should not be used in the closure of skin incisions since it may interfere with the healing of skin edges or cause wound dehiscence.

Hypersensitivity

Administration of TachoSil may result in allergic reactions in some patients. For patients with a known allergic diathesis or a history of hypersensitivity to protein products, a careful risk-benefit assessment should be carried out prior to administration. The risk of immunisation against proteins is increased if repeated exposure occurs within six months. If it is decided to proceed with treatment in such patients, prior administration of antihistamines should be considered.

Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration must be discontinued immediately. In case of shock, the current medical standards for shock treatment should be observed.

Contaminated Spaces

Do not leave TachoSil in an infected or contaminated space because it may potentiate an existing infection.

Transmissible infectious agents

The active substances of TachoSil are derived from human plasma. Products made from human plasma may contain infectious agents which can cause disease, such as viruses and theoretically Creutzfeld-Jacob Disease (CJD) agents. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include: selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parovirus B19. Parovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

It is therefore strongly recommended that every time TachoSil is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

All infections thought by a clinician possibly to have been transmitted by TachoSil should be reported by the clinician or other health care provider to Nycomed.

Patients should be instructed to consult their clinician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain).

Effects on Fertility

Studies to determine the effect of TachoSil on fertility have not been performed.

Use in Pregnancy (Category B2)

The safety of TachoSil for use in human pregnancy has not been established in controlled clinical trials. Therefore, TachoSil should be administered to pregnant women only if clearly needed.

Use in Lactation

It is not known whether this drug is excreted in human milk. Therefore, TachoSil should be administered to lactating women only if clearly needed.

Paediatric Use

TachoSil is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Use in the Elderly

In clinical trials, no overall differences in the safety or effectiveness of TachoSil were observed in patients over the age of 65, compared to patients 18 to 65 years of age.

Genotoxicity

Studies to determine the genotoxicity of TachoSil have not been performed.

Carcinogenicity

Long-term animal studies to evaluate the carcinogenic potential of TachoSil have not been performed.**Effects on laboratory tests**

Interactions with laboratory tests have not been established.

INTERACTIONS WITH OTHER MEDICINES

No formal interaction studies have been performed.

Similar to comparable products or thrombin solutions, TachoSil may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before application.

ADVERSE EFFECTS

Clinical Trials Experience

From six controlled trials, 521 patients were treated with TachoSil and 511 patients treated with comparator treatment. The only individual adverse events reported in more than 5% of patients in either treatment group were atrial fibrillation (32 patients [6.1%] in the TachoSil group and 30 patients [5.9%] in the comparator group) and pyrexia (30 patients [5.8%] in the TachoSil group and 25 patients [4.9%] in the comparator group).

A summary of all adverse events reported by at least 1% of patients and a classification of their severity is shown in Table 1. There are no notable differences in the severity of adverse events between the treatment groups and the majority of adverse events reported were mild or moderate in severity.

Table 1. Reported Severity of Adverse Events Experienced by at Least 1% of Patients in Either Treatment Group (All-trials Pool).

Adverse Event (Preferred Term)	**TachoSil N = 521**				**Comparator N = 511**			
	Mild	**Moderate**	**Severe**	**Any**	**Mild**	**Moderate**	**Severe**	**Any**
Atrial fibrillation	21 (4.0%)	9 (1.7%)	2 (0.4%)	32 (6.1%)	20 (3.9%)	10 (2.0%)	0	30 (5.9%)
Pyrexia	25 (4.8%)	5 (1.0%)	0	30 (5.8%)	18 (3.5%)	7 (1.4%)	0	25 (4.9%)
Pleural effusion	18 (3.5%)	5 (1.0%)	1 (0.2%)	24 (4.6%)	13 (2.5%)	6 (1.2%)	1 (0.2%)	20 (3.9%)
Pneumonia	10 (1.9%)	6 (1.2%)	0	16 (3.1%)	10 (2.0%)	9 (1.8%)	2 (0.4%)	21 (4.1%)
Nausea	8 (1.5%)	7 (1.3%)	0	15 (2.9%)	5 (1.0%)	4 (0.8%)	0	9 (1.8%)
Pneumothorax	9 (1.7%)	5 (1.0%)	0	14 (2.7%)	11 (2.2%)	7 (1.4%)	2 (0.4%)	20 (3.9%)
Constipation	9 (1.7%)	4 (0.8%)	1 (0.2%)	14 (2.7%)	14 (2.7%)	1 (0.2%)	0	15 (2.9%)
Respiratory failure	1 (0.2%)	0	6 (1.2%)	7 (1.3%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	4 (0.8%)
Tachyarrhythmia	9 (1.7%)	1 (0.2%)	1 (0.2%)	11 (2.1%)	5 (1.0%)	5 (1.0%)	1 (0.2%)	11 (2.2%)

Hypertension	4 (0.8%)	6 (1.2%)	1 (0.2%)	11 (2.1%)	6 (1.2%)	2 (0.4%)	1 (0.2%)	9 (1.8%)
Wound infection	7 (1.3%)	1 (0.2%)	2 (0.4%)	10 (1.9%)	4 (0.8%)	0	0	4 (0.8%)
Atelectasis	4 (0.8%)	5 (1.0%)	0	9 (1.7%)	7 (1.4%)	6 (1.2%)	1 (0.2%)	14 (2.7%)
Post-procedural haemorrhage	3 (0.6%)	3 (0.6%)	3 (0.6%)	9 (1.7%)	3 (0.6%)	4 (0.8%)	2 (0.4%)	9 (1.8%)
Anemia	4 (0.8%)	3 (0.6%)	1 (0.2%)	8 (1.5%)	6 (1.2%)	1 (0.2%)	0	7 (1.4%)
Pain	2 (0.4%)	4 (0.8%)	1 (0.2%)	7 (1.3%)	4 (0.8%)	1 (0.2%)	0	5 (1.0%)
Pruritus	6 (1.2%)	1 (0.2%)	0	7 (1.3%)	0	0	0	0
Hypotension	2 (0.4%)	4 (0.8%)	0	6 (1.2%)	3 (0.6%)	2 (0.4%)	2 (0.4%)	7 (1.4%)
Hyperglycemia	3 (0.6%)	3 (0.6%)	0	6 (1.2%)	2 (0.4%)	5 (1.0%)	0	7 (1.4%)
Sleep disorder	5 (1.0%)	1 (0.2%)	0	6 (1.2%)	3 (0.6%)	0	0	3 (0.6%)
Haemorrhagic anaemia	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (1.0%)	3 (0.6%)	3 (0.6%)	0	6 (1.2%)
Cystitis	5 (1.0%)	0	0	5 (1.0%)	3 (0.6%)	1 (0.2%)	0	4 (0.8%)
Dyspnoea	2 (0.4%)	3 (0.6%)	0	5 (1.0%)	3 (0.6%)	1 (0.2%)	0	4 (0.8%)
Insomnia	5 (1.0%)	0	0	5 (1.0%)	3 (0.6%)	0	0	3 (0.6%)
Myocardial infarction	2 (0.4%)	1 (0.2%)	2 (0.4%)	5 (1.0%)	0	0	2 (0.4%)	2 (0.4%)
Procedural site reaction	4 (0.8%)	0	1 (0.2%)	5 (1.0%)	0	1 (0.2%)	0	1 (0.2%)
Bronchopleural fistula	2 (0.4%)	1 (0.2%)	0	3 (0.6%)	6 (1.2%)	0	2 (0.4%)	8 (1.6%)
Flatulence	3 (0.6%)	0	0	3 (0.6%)	8 (1.6%)	0	0	8 (1.6%)
Urinary tract infection	2 (0.4%)	2 (0.4%)	0	4 (0.8%)	8 (1.6%)	1 (0.2%)	0	9 (1.8%)
Vocal cord paralysis	1 (0.2%)	0	0	1 (0.2%)	3 (0.6%)	2 (0.4%)	0	5 (1.0%)
Haemoglobin decreased	0	0	0	0	5 (1.0%)	0	0	5 (1.0%)

Note: This table represents the number of patients experiencing at least one adverse reaction regardless of causality. At each level of patient summarisation, a patient is counted only once for the most severe occurrence if the patient reported one or more events. Percentages are based on the number of patients in each treatment group.

DOSAGE AND ADMINISTRATION

The use of TachoSil is restricted to experienced surgeons.

TachoSil should not be used intravascularly (see 'Contraindications'). For more information on situations where TachoSil should not be used, see 'Precautions'.

The number of TachoSil sponges to be applied should always be orientated towards the underlying clinical need for the patient and should be governed by the size of the wound area.

Application of TachoSil must be individualised by the treating surgeon. In clinical trials, the individual dosages have typically ranged from 1 to 2 sponges (9.5 cm x 4.8 cm), however application of up to 7 sponges has been reported. For smaller wounds, e.g. in minimal invasive surgery, the smaller sized sponges (4.8 cm x 4.8 cm or 3.0 cm x 2.5 cm) are recommended.

TachoSil comes ready to use in sterile packages and must be handled accordingly. Use only undamaged packages. Once the package is opened, re-sterilisation is not possible. The outer aluminium foil sachet may be opened in a non-sterile operating area but the inner

sterile blister must be opened in a sterile operating room area. TachoSil should be used immediately after opening the inner sterile cover.

TachoSil should be used under sterile conditions. Prior to application the wound area should be cleansed, e.g. from blood, disinfectants and other fluids. After removal of TachoSil from the sterile package the sponge may be pre-moistened in saline solution for no more than 1 minute and then applied immediately. The yellow, active side of the sponge is applied to the bleeding/leaking surface and held against it with gentle pressure for 3 to 5 minutes. This procedure enables adhesion of TachoSil to the wound surface. Pressure is applied with moistened gloves or a moist pad. Due to the strong affinity of collagen to blood, TachoSil may also stick to surgical instruments or gloves covered with blood. This can be avoided by pre-moistening surgical instruments and gloves with physiological saline solution. After pressing TachoSil to the wound, the glove or the pad must be removed carefully. To avoid the sponge from being pulled loose it may be held in place at one end, e.g. with a pair of forceps.

Alternatively, e.g. in case of stronger bleeding, TachoSil may be applied without pre-moistening, while also pressing gently to the wound for 3 to 5 minutes.

The TachoSil sponge should be applied so that it extends 1 to 2 cm beyond the margins of the wound. If more than one sponge is used the sponges should overlap. The sponge can be cut to the correct size and shaped if too large.

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

No case of overdose has been reported.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

TachoSil is an off white sponge. The active side of the sponge, which is coated with human fibrinogen and thrombin, is marked by a yellow colour.

Three sizes are available in the following dimensions (length x width):

Standard size:	9.5 cm x 4.8 cm = 45.6 cm^2, containing human thrombin 91.2 IU and human fibrinogen 250.8 mg
Midi size:	4.8 cm x 4.8 cm = 23.0 cm^2, containing human thrombin 46.0 IU and human fibrinogen 126.5 mg
Mini size:	3.0 cm x 2.5 cm = 7.5 cm^2, containing human thrombin 15.0 IU and human fibrinogen 41.3 mg

The composition is the same for all three presentations with each square centimetre containing 5.5 mg human fibrinogen and 2.0 IU human thrombin.

Each TachoSil medicated sponge is packaged individually in a blister sealed with a HDPE foil. The blister is packed in an aluminium-bonded foil sachet, with a desiccant bag. Once the foil sachet is opened, TachoSil must be used immediately.

The following pack sizes are available:

Package with 1 sponge of 9.5 cm x 4.8 cm
Package with 2 sponges of 4.8 cm x 4.8 cm
Package with 1 sponge of 3.0 cm x 2.5 cm
Package with 5 sponges of 3.0 cm x 2.5 cm

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Nycomed Pty Ltd
2-4 Lyonpark Rd
North Ryde NSW 2113
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG) 22 March 2012