PRODUCT MONOGRAPH

TachoSil®

absorbable fibrin sealant patch

5.5 mg Human Fibrinogen, 2.0 IU Human Thrombin and 2.1 mg Collagen Sponge per cm^2

Hemostatic Agent

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TACHOSIL®

absorbable fibrin sealant patch

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	absorbable fibrin sealant patch / per cm^2: Human Fibrinogen 5.5 mg Human Thrombin 2.0 IU Collagen Sponge 2.1 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.*

DESCRIPTION

TachoSil® (Human Thrombin, Human Fibrinogen absorbable collagen fibrin sealant patch) is a ready-to-use degradable surgical patch. TachoSil® consists of a whitish, closed cell (honeycomb) equine Collagen Sponge coated on one side with the active ingredients Human Fibrinogen (human sealer protein) and Human Thrombin. Riboflavin is included in the coating mixture as a yellow colorant to signify the active side. Each square centimetre contains 5.5 mg of Human Fibrinogen, 2.0 units (IU) of Human Thrombin and 2.1 mg Collagen Sponge.

Each fibrin sealant patch is packaged in an appropriately sized blister pack of PET-GAG formed foil and HDPE foil and overwrapped with an aluminium laminate foil pack with a desiccant bag.

The manufacturing procedure of TachoSil® and its active substances includes processing steps designed to reduce the risk of viral transmission. In particular, pasteurization, precipitation and adsorption steps are included in the manufacturing of fibrinogen and thrombin and pH treatment in the manufacturing of the collagen sponge. Validation studies for fibrinogen, thrombin and collagen sponge manufacturing steps were conducted for their capacity to inactivate and/or remove viruses.

TachoSil® is sterilized by gamma irradiation after completion of inner and outer packaging, resulting in a sterile product in a sterile inner package. A validation study was conducted evaluating the capacity of gamma irradiation to inactivate viruses.

INDICATIONS AND CLINICAL USE

TachoSil® is indicated in adults for supportive treatment in surgery for improvement of hemostasis, and for suture support in vascular surgery where standard techniques are insufficient.

Geriatrics (> 65 years of age):
Efficacy and safety of TachoSil® has been evaluated in 204 patients of 65 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatrics (<18 years of age):
The safety and effectiveness of TachoSil® in pediatric patients have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to the active substances or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

TachoSil® must not be applied intravascularly.

WARNINGS AND PRECAUTIONS

When medicinal products manufactured from human plasma are administered, the possibility of transmission of infective agents cannot be totally excluded. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patients (see WARNINGS AND PRECAUTIONS, Transmissible Infectious Agents section).

General

TachoSil® is intended for topical use only by experienced surgeons. Do not use intravascularly. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Ensure tissue areas outside the desired application site are adequately cleansed before TachoSil administration, in order to prevent the development of tissue adhesions at undesired sites (see DOSAGE AND ADMINISTRATION, Administration). Events of adhesions to gastrointestinal tissues leading to gastrointestinal obstruction have been reported with use in abdominal surgery carried out in proximity to the bowel.

Hypersensitivity/ Allergic/ Anaphylactic Reactions

As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, the current medical standards for shock treatment should be observed.

Transmissible Infectious 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 and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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 parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Arterial Bleeding

Do not use TachoSil® for the treatment of severe or brisk arterial bleeding because TachoSil® has not been evaluated in this treatment.

Primary Hemostasis

Do not use TachoSil® as the primary mode to control hemostasis. TachoSil® is not intended as a substitute for meticulous surgical technique and the proper application of suture, ligature or other conventional procedures for hemostasis.

Contaminated Spaces

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

Closed Spaces

When placing TachoSil® into cavities or closed spaces, avoid over-packing because this may cause compression of underlying tissue. Use only the minimum amount of TachoSil® patches necessary to achieve hemostasis. Carefully remove or reposition unattached pieces of TachoSil®, if medically necessary.

Limitations of TachoSil® Use

Do not use TachoSil® in neurosurgical or gastrointestinal anastomosis procedures as safety and efficacy has not been evaluated.

Special Populations

Pregnant Women: The safety of fibrin sealants/haemostatics for use in human pregnancy has not been established in controlled clinical trials.

Nursing Women: The safety of fibrin sealants/haemostatics for use in nursing women has not been established in controlled clinical trials.

Pediatrics (<18 years of age):
The safety and effectiveness of TachoSil® in pediatric patients have not been established.

Geriatrics (> 65 years of age):
Efficacy and safety of TachoSil® has been evaluated in 204 patients of 65 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions reported in clinical trials (determined by investigators) were experienced by 6.9% of patients treated with TachoSil® compared to 7.2% of patients treated with comparator treatments. The most common adverse drug reaction was pyrexia, which occurred in 2.5% of TachoSil® treated patients and 2.0% of comparator treated patients.

Rarely, hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in patients treated with fibrin sealants/ hemostatics. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. Antibodies against components of fibrin sealant/hemostatic products may occur rarely. The equine collagen antibodies that developed in some patients after TachoSil® use were not reactive with human collagen. One patient developed antibodies to human fibrinogen. There were no adverse events attributable to the development of human fibrinogen or equine collagen antibodies. There is very limited clinical data available regarding re-exposure of TachoSil®. Thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of TachoSil® has been evaluated in six controlled clinical trials, in which 521 patients were treated with TachoSil® and 511 patients were treated with comparator treatment. Due to practical reasons (comparison to standard surgical and standard hemostatic treatment), blinding was not possible in the TachoSil® trials. Therefore, the studies were performed as open-label studies.

The most common adverse drug reaction reported in these clinical trials was pyrexia, which occurred in 2.5% of TachoSil® treated patients and 2.0% of comparator treated patients.

Adverse drug reactions occurring in these clinical trials involving TachoSil® with an incidence of less than 1% include the following:

Cardiac disorders: Tachyarrhythmia
Gastrointestinal disorders: Abdominal pain, Flatulence
General disorders and administration site conditions: Pain, Drug ineffective
Infections and infestations: Liver abscess, Post-operative abscess, Wound abscess

Injury, poisoning, procedural complaints: Procedural site reaction, Anemia post-operative, Post-procedural hemorrhage
Investigations: C-reactive protein increased
Psychiatric disorders: Insomnia, Nervousness
Renal and urinary disorders: Renal disorder, Urinary retention
Respiratory, thoracic and mediastinal disorders: Pneumothorax, Pleural effusion, Lung disorder, Bronchopleural fistula, cough
Skin and subcutaneous tissue disorders: Pruritus, urticaria
Vascular disorders: Hypertension

In addition, a safety surveillance trial was performed with 3098 patients (mean age: 60.7, range: 0.1 - 94 years of age) to collect information, following exposure to TachoSil®, of all thromboembolic events, immunological events and drug interactions leading to thromboembolic events or major bleeding. The trial was designed as an international, non-interventional, prospective, single cohort trial of the use of TachoSil® in supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient. The majority of patients (90.8%) had at least one risk for thromboembolic events before surgery (8.2% had risk factors for major bleeding and 15.3% had risk factors for immunological events). At any time during the trial 1.5% (95% CI 1.1%-2.0%), 2.0% (95% CI 1.5-2.6%) and 0.3% of patients had at least one thromboembolic, major bleeding, or immunological event, respectively. No cases were reported where an investigator suspected an interaction with concomitant medication as responsible for an adverse event.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been reported in post-marketing experience:

Immune disorders: Anaphylactic shock, hypersensitivity
Gastrointestinal disorders: Intestinal obstruction (in abdominal surgeries), ileus (in abdominal surgeries)
General disorders and administration site conditions: Adhesions, Drug ineffective
Vascular disorders: Thrombosis

Because post-marketing reporting of adverse reaction is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

DRUG INTERACTIONS

Overview

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 applying TachoSil®.

DOSAGE AND ADMINISTRATION

Dosing and Administrative Considerations

TachoSil® is intended for topical use only. Do not use intravascularly.
Apply the yellow, active side of the patch to the bleeding area.

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

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 sterile physiological saline solution.

Recommended Dose

The number of TachoSil® patches to be applied should always be oriented towards the underlying clinical need for the patient. The number of TachoSil® patches to be applied is governed by the size of the wound area.

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

Open, unused TachoSil® should be discarded as it cannot be re-sterilized.

Application of TachoSil® must be individualized by the treating surgeon. In clinical trials, the individual dosages have typically ranged from 1-3 patches (9.5 cm x 4.8 cm); application of up to 7 patches has been reported. For smaller wounds, e.g. in minimal invasive surgery the smaller size patches (4.8 cm x 4.8 cm or 3.0 cm x 2.5 cm) are recommended.

TachoSil® Patch size	**Amount of Human Fibrinogen / Total Patch Size (mg)***	**Amount of Human Thrombin / Total Patch Size (IU)***
3.0 cm x 2.5 cm	41.3	15.0
4.8 cm x 4.8 cm	126.5	46.0
9.5 cm x 4.8 cm	250.8	91.2

* Each square centimetre contains: 5.5 mg Human Fibrinogen and 2.0 IU Human Thrombin

Administration

TachoSil® is used under sterile conditions. Prior to application the wound area should be cleansed, e.g. from blood, disinfectants and other fluids. The fibrinogen and thrombin proteins can be denatured by alcohol, iodine or heavy metal ions. If any of these substances have been used to clean the wound area, thoroughly irrigate the area before the application of TachoSil®. It is important to note that failure to adequately clean adjacent tissues may cause adhesions.

After removal of TachoSil® from the sterile package the patch should be pre-moistened in sterile saline solution. Once moistened TachoSil® should be applied immediately.

The yellow, active side of the patch is applied to the bleeding surface and held against it with a gentle pressure for 3-5 minutes. This procedure enables an easy adhesion of TachoSil® to the wound surface. Alternatively, e.g. in case of stronger bleeding or wet wound area,

TachoSil® may be applied without pre-moistening, while also pressing gently to the wound for 3-5 minutes. It is recommended that a moist surgical tissue or pad is used for applying pressure if TachoSil® is applied dry.

Pressure should be applied with moistened gloves or a moist pad. After pressing TachoSil® to the wound, the glove or the pad must be removed carefully. To avoid the patch from being pulled loose it may be held in place at one end, e.g. with a pair of forceps.

Leave TachoSil® in place once it adheres to organ tissue. Remove unattached TachoSil® patches (or part of) and replace with new patches.

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

OVERDOSE

No cases of overdose have been reported.

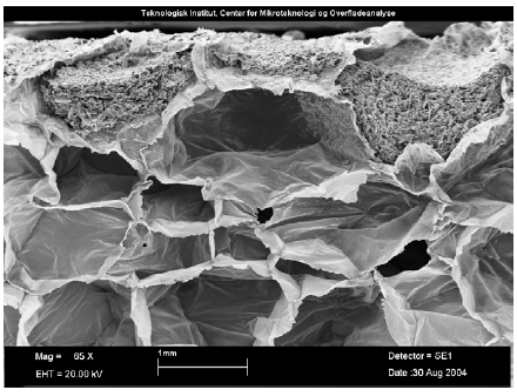
For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

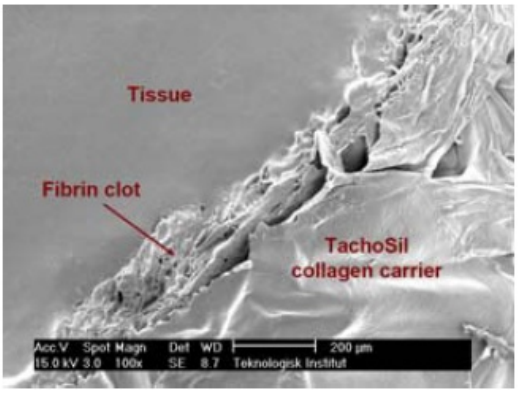
Mechanism of Action

TachoSil® is a ready to use degradable surgical patch consisting of a Collagen Sponge of equine origin, coated with Human Fibrinogen and Human Thrombin (Figure 1a). In contact with physiological fluids, e.g. 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 (i.e. coagulation cascade). Fibrinogen is converted into fibrin monomers which spontaneously polymerize to a fibrin clot, which holds the Collagen Sponge tightly to the wound surface. The fibrin is then cross linked by endogenous factor XIII, creating a firm, mechanically stable network with strong adhesive properties (Figure 1b). The active components of TachoSil® cause the wound surface and the patch to be adhered together. TachoSil® exhibits flexibility to accommodate for the physiological movements of tissues and organs.

Figure 1. Scanning Electron Microscopy pictures of TachoSil®



a) Side view of TachoSil®, showing the coating of fibrinogen and thrombin anchored to the indentations of the Collagen Sponge.



b) Deposition of a fibrin clot formed from the fibrinogen and thrombin causes hemostasis, and adhesion of the TachoSil® patch to the tissue wound.

Pharmacodynamics

No pharmacodynamic studies have been performed with TachoSil® in man. Clinical Studies demonstrating hemostasis have been conducted in four controlled clinical trials (see CLINICAL TRIALS).

Pharmacokinetics

TachoSil® is intended for topical application only (i.e. for application on the surface of tissue), and intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

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

STORAGE AND STABILITY

TachoSil® should be stored at 2 to 30 °C.
TachoSil® does not require refrigeration. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

none

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each patch is packed in a PET-GAG blister sealed with a coated PE foil. The blister is packed in an aluminium-bonded foil sachet with a desiccant bag. Each patch is packaged individually.

TachoSil® is supplied in the following pack sizes:
Package with 1 patch of 9.5 cm x 4.8 cm
Package with 2 patches of 4.8 cm x 4.8 cm
Package with 1 patch of 3.0 cm x 2.5 cm
Package with 5 patches of 3.0 cm x 2.5 cm

Not all pack sizes may be marketed.

TachoSil® contains the following non-medicinal ingredients: Human albumin, Riboflavin (E 101), Sodium chloride, Sodium citrate (E331), L-arginine-hydrochloride.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Human Thrombin
Human Fibrinogen
Collagen Sponge

Chemical name: Not applicable

Molecular formula and molecular mass:
Human Thrombin: 39 kDa
Human Fibrinogen: 340 kDa
Collagen (tropocollagen): ~ 300 kDa

Structural formula: Not applicable

Product Characteristics

Human Fibrinogen and Human Thrombin are obtained from pooled human plasma obtained from US licensed plasma collection centres. The Collagen Sponge is of equine origin.

Fibrinogen

Fibrinogen is manufactured by treatment of cryoprecipitate for purification of fibrinogen. The preparation is treated by pasteurization, following which it is precipitated, and concentrated. After concentration the product is formulated, 0.2µm filtered, aseptically filled and lyophilized.

Thrombin

Thrombin is manufactured by chromatographic purification of pro-thrombin from cryo-poor plasma. The preparation is pasteurized and precipitated. The pro-thrombin is converted to thrombin, and the preparation is concentrated, 0.2µm filtered, aseptically filled and lyophilized.

Collagen Sponge

Collagen Sponge is a whitish, sponge-like material cut into the form of strips. Collagen Sponge is intended for use as a carrier for further manufacture of TachoSil.

TachoSil

TachoSil consists of a whitish equine Collagen Sponge coated with the active ingredients Human Fibrinogen and Human Thrombin, and riboflavin as yellow colorant.

Viral Inactivation

Validation studies for fibrinogen, thrombin and Collagen Sponge manufacturing steps were conducted for their capacity to inactivate and/or remove viruses. These in vitro validation studies were conducted, using samples from manufacturing intermediates spiked with virus suspensions of known titres followed by further processing under conditions equivalent to those in the respective manufacturing steps.

TachoSil® is sterilized by gamma irradiation after completion of inner and outer packaging, resulting in a sterile product in a sterile inner package. A validation study was conducted evaluating the capacity of gamma irradiation to inactivate viruses.

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and efficacy of TachoSil® were assessed in four open-label, randomized, prospective, multicentre, controlled studies (Table 1). TachoSil® was used as secondary management for improvement of hemostasis, and for suture support in vascular surgery where standard techniques are insufficient.

Due to practical reasons (comparison to standard surgical and standard hemostatic treatment), blinding was not possible in the TachoSil® trials. Therefore the studies were performed as open-label studies.

The TachoSil® patch used in these studies was 9.5 cm x 4.8 cm.

Table 1. Summary of Patient Demographics for Pivotal Clinical Trials

Study #	Surgical indication	Study treatment randomized and number of subjects	Mean age (Range)	Gender (Male:Female)
TC-014-IN	Liver resection	TachoSil®: 59 Argon beam coagulator: 62	56.1 (19 – 78) 57.1 (18 – 81)	46% : 54% 61% : 39%
TC-015-IN	Kidney resection	TachoSil®: 92 Standard surgical treatment (additional suturing if needed): 93	61.5 (23 – 81) 64.3 (42 – 84)	67% : 33% 61% : 39%
TC-016-IN	Liver resection	TachoSil®: 60 Argon beam coagulator: 59	59.2 (19 – 82) 59.8 (28 – 76)	67% : 33% 51% : 49%
TC-023-IM	Cardiovascular surgery	TachoSil®: 59 Hemostatic fleece:60	65 (23 – 82) 68 (36 – 86)	76% : 24% 72% : 28%

Study results
The efficacy and safety of TachoSil® as a supportive treatment in surgery for the improvement of hemostasis, and for suture support was investigated in four pivotal studies. These studies demonstrated the efficacy and safety of TachoSil®, as a hemostasic agent.

Study TC-014-IN and Study TC-016-IN
Two trials (TC-014-IN and TC-016-IN) investigated the efficacy and safety of TachoSil® as an adjunct treatment to control haemorrhage from the resection wound following segmental liver resection. The trials were designed as randomized, open, parallel-group, multi-centre trials comparing the efficacy and safety of TachoSil® vs. the argon beam coagulator (argon beamer). Patients were undergoing resection of the liver for any medical reason, most related to hepatic malignancies. Randomization, to either TachoSil® or argon beamer, was done 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. The primary efficacy outcome of both trials was the intra-operative assessment of time to hemostasis, which was measured from the time when randomized treatments (TachoSil® or argon beam coagulator) were applied.

In trial TC-014-IN, 59 patients in the TachoSil® group received 156 TachoSil® patches. The majority of the patients had 1 to 4 patches, 2 patients had 5 patches, and 2 patients had 6 patches. In trial TC-016-IN, 60 patients in the TachoSil® group received 143 TachoSil® patches. The majority of the patients had 1 to 4 patches, 2 patients had 5 patches, 1 patient had 6 patches, and 1 patient had 7 patches.

Both trials, TC-014-IN and TC-016-IN, demonstrated statistically significant superiority of TachoSil® over the control treatment (p=0.0007 & p=0.0018, respectively)(Table 2). The results clearly showed TachoSil® to be efficacious in the treatment of the diffuse bleeding condition often present in liver surgery, with a shorter time to hemostasis than the argon beam coagulator.

Table 2. Trial TC-014-IN and TC-016-IN Primary Efficacy Endpoint – Time to Hemostasis

	TachoSil® Time to Hemostasis (minutes)		**Argon Beam Coagulator Time to Hemostasis (minutes)**		**p-value**
	mean	**median (range)**	**mean**	**median (range)**	
TC-014-IN	3.9	3.0 (3-20)	6.3	4.0 (3-39)	0.0007*
TC-016-IN	3.6	3.0 (3-8)	5.0	3.0 (3-23)	0.0018*

* statistically significant

Study TC-015-IN
Trial TC-015-IN investigated the hemostatic efficacy of TachoSil® compared to standard surgery in patients scheduled for the resection of superficial tumours on the kidney. Patients in the trial underwent nephron-sparing surgery. The trial was an open-label, randomized, prospective, multi-centre, parallel-group trial to compare the efficacy and safety of additional TachoSil® vs. standard surgical treatment alone in patients undergoing surgical resection of superficial renal tumour. Randomisation was done following the resection of superficial solitary kidney tumour and primary standard hemostatic measures to control pulsating arterial

and/or major venous hemorrhage. The primary efficacy endpoint was the intra-operative time to hemostasis.

A total of 92 patients in the TachoSil® group received 116 TachoSil® patches. The majority of the patients had 1 to 2 patches, and 3 patients had 3 patches.

The primary efficacy endpoint, time to hemostasis, demonstrated a clear statistically significant difference ($p<0.0001$) for additional TachoSil® over standard suturing alone with median values of 3.0 minutes (mean 5.3 min; range 3-17 min) and 8.0 minutes (mean 9.5 min; range 3-27 min), respectively for the ITT population.

Study TC-023-IM

A cardiovascular trial, TC-023-IM, was designed as a randomized, open, parallel-group, multi-centre trial comparing the efficacy and safety of TachoSil® vs. standard hemostatic fleece (without additional active coagulation stimulating compounds) in cardiovascular surgery. Patients undergoing a planned elective surgery on the heart, the ascending aorta or aortic arch requiring a cardiopulmonary bypass procedure were included in this trial. Patients were equally distributed to the two treatment arms, TachoSil® or standard hemostatic treatment (i.e. any hemostatic fleece material without additional active coagulation-stimulating compounds). Randomisation was done during surgery, following primary hemostatic treatment when intra-operative bleeding had been assessed. Only patients with residual hemorrhage from the heart muscle, the pericardium, a major vessel or vascular bed requiring supportive hemostatic treatment were eligible for randomization. Patients included were required to be on cardiopulmonary bypass during surgery (i.e. fully heparinized patients).

Hemostasis in the target area was evaluated after 3 minutes of application with pressure. If hemostasis was achieved, “time to hemostasis” was recorded as 3 minutes. If hemostasis was not achieved, another piece of trial treatment (TachoSil® or standard fleece material) was applied for the next 3 minutes. The primary and secondary efficacy endpoints were the proportion of patients that achieved hemostasis at 3 minutes and 6 minutes, respectively.

A total of 62 patients in the TachoSil® group received 74 TachoSil® patches. The majority of the patients had 1 patch, 7 patients had 2 patches, 1 patient had 3 patches, and 1 patient had 4 patches.

The results showed that TachoSil® was statistically significantly superior to standard fleece material with regard to the primary and secondary endpoints of the trial (Table 3). The proportion of patients with hemostasis at 3 minutes was 75% for TachoSil® patients and 33% for standard hemostatic fleece patients ($p<0.0001$). The proportion of patients with hemostasis at 6 minutes confirmed this with significant results in favour of TachoSil® ($p=0.0006$).

Table 3. Trial TC-023-IM Primary and Secondary Endpoints – Proportion of Patients with Hemostasis at 3 and 6 minutes

Treatment	Number of patients with hemostasis	Proportion of patients with hemostasis	95% CI for proportion	p-value
Hemostasis at 3 min				
TachoSil® (n=59)	44	0.746 (75%)	[0.635; 0.857]	<0.0001*
Standard (n=60)	20	0.333 (33%)	[0.214; 0.453]	
Hemostasis at 6 min				
TachoSil® (n=59)	56	0.949 (95%)	[0.893; 1.000]	<0.0006*
Standard (n=60)	43	0.717 (72%)	[0.603; 0.831]	

*statistically significant
CI= confidence interval

DETAILED PHARMACOLOGY

Animal Pharmacology

One *in vivo* study in rats confirmed that the concentration of fibrinogen and thrombin in TachoSil® are optimal to achieve maximum adhesive strength to the wound surface. Animal models (in rat, rabbit, dog, and pig) have shown TachoSil® to be effective in achieving hemostatic wound sealing, independent of the organ applied to, and in various challenge models (high blood pressure, hyperfibrinolytic, hypocoagulability status, increased enzymatic degradation in pancreatitis).

TOXICOLOGY

Single-dose Toxicity

The single-dose toxicity of TachoSil® has been investigated in mini-pigs after topical application to liver and/or spleen lesions via laparotomy.

One single-dose study investigated the toxicity of TachoSil® in minipigs following application to liver and spleen wounds at a physiological dose of 48.5 mg/kg (2.3 times the average clinical dose for humans [2 patches/ 70 kg patient; 21 mg/kg]). Necropsy was performed 1, 4 and 13 weeks after TachoSil® administration. No deaths occurred, there were no drug product-related toxicological effects on body weight, food consumption, hematological parameters (including coagulation), clinical chemistry parameters, and organ weights. Compound remnants were still observed at the surgical site of the treated animals after 13 weeks. The observed macroscopical and microscopial findings showed the regulator process of biodegradation, fibrinolysis and phagocytosis, and are not considered to be of any toxicological significance.

A second single-dose study investigated the toxicity of TachoSil® in minipigs following application to liver wounds at a dose of up to 202.2 mg/kg, which is about 9.6 times the average clinical dose (2 patches/ 70 kg patient; 21 mg/kg). Necropsy was performed 26 and

52 weeks after TachoSil® administration. No deaths occurred. There were no drug product-related toxicological effects on body weight, food consumption, hematological parameters (including coagulation), clinical chemistry parameters, and organ weights. TachoSil® had no effect on systemic safety after 12 months. Complete degradation of TachoSil® was seen in some animals 12 months after its administration to a liver wound, whereas small remnants were still observed in others. No evidence of local intolerability has been observed.

A third single-dose study investigated the toxicity of TachoSil® in minipigs following application of either 10 (440.8 mg/kg) or 15 (581.4 mg/kg) standard size patches onto liver lesions (up to 28 times than the average clinical dose [2 standard size patches/70 kg patient; 21 mg/kg]). This dose was 7.9 times higher than the maximum dose ever reported from a clinical trial (7 standard size patches per 70 kg patient; 73.2 mg/kg). No deaths occurred. Necropsy was performed after 2 weeks of TachoSil administration. There was no evidence of either local or systemic toxicity after administration of 15 patches (581.4 mg/kg) of TachoSil. This dose was the No Observable Effect Level (NOAEL) and the maximum feasible dose to be investigated in minipigs.

Repeat-dose Toxicity

A 4-week repeat-dose toxicity study was performed with TachoSil® in a liver/spleen lesion model in minipigs. In a surgical procedure a liver lesion was created on Day 1 a single standard size TachoSil® patch was applied to the wound. On Day 2, a second standard size TachoSil® patch was applied onto the same liver wound. On Day 22, a spleen lesion was created and one standard size TachoSil® patch was applied onto the wound. The cumulative final doses administered were 79.14 mg/kg TachoSil®. Necropsy was performed 7 and 28 days after the last administration to the spleen. No deaths occurred and there were no drug product-related toxicological effects on body weight, food consumption, hematological parameters (including coagulation), clinical chemistry parameters, and organ weights. Histological investigations showed that the TachoSil® patch becomes encased in granulation tissue containing many macrophages, some eosinophils lymphocytes and occasionally giant cells. The NOAEL for TachoSil® in the minipig following repeated administration, was 79.14 mg/kg, which is about 4-fold higher than the dose indicated for use in humans (2 patches/ 70 kg patient; 21 mg/kg).

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PART III: CONSUMER INFORMATION

TachoSil®
Human Thrombin, Human Fibrinogen and Collagen absorbable fibrin sealant patch

This leaflet is part III of a three-part "Product Monograph" published when TachoSil® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TachoSil®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TachoSil® is used during surgery to stop local bleeding (hemostasis) on internal organs.

What it does:
The yellow side of the TachoSil® patch contains the active components: human sealer protein (fibrinogen) and thrombin. The yellow side of the patch is therefore the active side. When the patch comes into contact with fluids (such as blood, lymph or saline solution) the fibrinogen and the thrombin are activated and form a fibrin network. This means that the patch sticks to the tissue surface, the blood coagulates (local hemostasis). In the body TachoSil® will dissolve and disappear completely.

When it should not be used:
TachoSil® should not be used in those who are allergic (hypersensitive) to the active components or any of the other ingredients of TachoSil®.

TachoSil® must not be applied inside a blood vessel.

What the medicinal ingredient is:
human fibrinogen (5.5 mg per cm^2), and human thrombin (2.0 IU per cm^2) and collagen (2.1 mg per cm^2)

What the nonmedicinal ingredients are:
human albumin, riboflavin (E101), sodium chloride, sodium citrate (E331) and L-arginine-hydrochloride.

What dosage forms it comes in:
TachoSil® is a patch made of collagen, which is coated on the yellow side with human fibrinogen and human thrombin. TachoSil® is available in three different sizes: 9.5 cm x 4.8 cm, 4.8 cm x 4.8 cm, and 3.0 cm x 2.5 cm.

WARNINGS AND PRECAUTIONS

TachoSil® is for local use only by experienced surgeons and should not be applied inside a blood vessel. Blood clots may occur if TachoSil® is unintentionally applied inside a blood vessel.

It is possible that you could suffer an allergic reaction after TachoSil® has been applied. If you experience hives, or a rash similar to nettle rash, chest discomfort or tightness, wheezing or low blood pressure, you should contact your doctor immediately.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to the patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant woman (fetal infection) and for individuals whose immune system is depressed or who have some types of anemia, (e.g. sickle cell disease or hemolytic anemia).

INTERACTIONS WITH THIS MEDICATION

No interaction studies have been performed.

PROPER USE OF THIS MEDICATION

The doctor treating you will administer TachoSil® during surgery. The doctor will place the patch on the internal organ to stop the bleeding. The number of TachoSil® patches used depends on the size of the wound. During the following time the patch will dissolve and disappear completely.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TachoSil® can cause side effects although not everybody gets them.

TachoSil® is made on the basis of human blood. All medicines based on human blood may rarely cause allergic reactions. In isolated cases these allergic reactions may progress to anaphylactic shock. These allergic reactions may occur especially if TachoSil® is used repeatedly or if you are allergic to any of the ingredients in TachoSil®. In rare cases antibodies can be produced against the active substances of TachoSil®.

Like following all surgery, you may experience a fever with TachoSil®.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

HOW TO STORE IT

Store TachoSil® at 2 to 30°C.

TachoSil® is to be kept out of the reach of children.

Do not use TachoSil® after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.takedacanada.ca or by contacting the sponsor, Takeda Canada Inc., at: 1-866-295-4636

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