PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

TachoSil sealant matrix.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TachoSil sealant matrix contains per cm^2:

Human Fibrinogen	5.5 mg
Human Thrombin	2.0 IU

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sealant matrix
TachoSil is an off-white sealant matrix. The active side of the matrix, which is coated with fibrinogen and thrombin, is marked by a yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient (see section 5.1).

4.2 Posology and method of administration

Posology
The use of TachoSil is restricted to experienced surgeons.

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

Application of TachoSil must be individualised by the treating surgeon. In clinical trials, the individual dosages have typically ranged from 1-3 units (9.5 cm x 4.8 cm); application of up to 10 units has been reported. For smaller wounds, e.g. in minimal invasive surgery the smaller size matrices (4.8 cm x 4.8 cm or 3.0 cm x 2.5 cm) are recommended.

Method and route of administration
For epilesional use only. Do not use intravascularly

See section 6.6 for more detailed instructions.

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

4.3 Contraindications

TachoSil must not be applied intravascularly
Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For epilesional use only.

Do not use intravascularly. Life threatening thromboembolic complications may occur if the preparation is applied intravascularly

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

It is not known whether recent radiation therapy affects the efficacy of TachoSil when used for dura mater sealing.

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately.

To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before administration of TachoSil (see section 6.6). 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.

In case of shock, the current medical standards for shock treatment should be observed.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

4.5 Interactions with other medicinal products and other forms of interactions

No formal interaction studies have been performed.
Similar to comparable products or thrombin solutions, the sealant 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 the sealant.

4.6 Pregnancy and lactation

The safety of TachoSil for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development.

Therefore, TachoSil should be administered to pregnant and lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. 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.

<u>Immunogenicity:</u>

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.
However, in a clinical trial with TachoSil in hepatic surgery, in which patients were investigated for the development of antibodies, 26% of the 96 patients tested and treated with TachoSil developed antibodies to equine collagen. 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. Two subjects have been re-exposed in a clinical trial and have not reported any immune-mediated adverse events, however, their antibody status to collagen or fibrinogen is unknown.

Thromboembolic complications may occur if the preparation is applied intravascularly (see section 4.4)

For viral safety see section 4.4.

Summary of the safety profile

The safety data of TachoSil generally reflect the type of post-operative complications related to the surgical settings in which the trials were conducted and the underlying disease of the patients.

Data from the eight controlled clinical trials conducted by the MAH has been pooled into an integrated dataset. In the integrated analyses, 997 patients were treated with TachoSil and 984 patients were treated with comparator treatment. Due to practical reasons (comparison to standard surgical and standard haemostatic treatment), blinding was not possible in the TachoSil trials. Therefore the studies were performed as open-label studies.

Tabulated summary of adverse reactions

The following adverse reactions have been reported with TachoSil during post marketing experience. The frequency of all of the events listed below has been categorised as not known (cannot be estimated from the available data).

System organ class	**Frequency not known**
Immune system disorders	Anaphylactic shock, Hypersensitivity
Vascular disorders	Thrombosis
Gastrointestinal disorders	Intestinal obstruction (in abdominal surgeries)
General disorders and administration site conditions	Adhesions

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

No case of overdose has been reported**.**

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group: Local haemostatics, ATC code: B02BC30

TachoSil contains fibrinogen and thrombin as a dried coating on the surface of a collagen matrix. 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. Fibrinogen is converted into fibrin monomers which spontaneously polymerise to a fibrin clot, which holds the collagen matrix tightly to the wound surface. The fibrin is then cross linked by endogenous factor XIII, creating a firm, mechanically stable network with good adhesive properties and provides sealing as well.

Clinical studies demonstrating haemostasis were conducted in a total of 240 patients (119 TachoSil, 121 argon beamer) undergoing partial liver resection surgery and 185 patients (92 TachoSil, 93 standard surgical treatment) undergoing surgical resection of superficial renal tumour. A further controlled study in 119 patients (62 TachoSil, 57 haemostatic fleece) demonstrated sealing, haemostasis and suture support in patients undergoing cardiovascular surgery. Tissue sealing in lung surgery was investigated in two controlled trials in patients undergoing lung surgery. The first controlled clinical trial investigating tissue sealing in lung surgery failed to document superiority over standard treatment measured by air leakage due to the inclusion of a large group of patients (53%) without air leakage. However, the second study investigating tissue sealing in 299 patients (149 TachoSil, 150 standard surgical

treatment) with demonstrated intraoperative air leakage showed the superiority of TachoSil compared to standard treatment.

The efficacy of TachoSil was tested in a randomised controlled study in 726 patients (362 treated with TachoSil and 364 controls) undergoing skull base surgery as an adjunct to suture for sealing the dura mater, in which the efficacy outcome was measured post-operatively as verified cerebrospinal fluid (CSF) leaks or pseudomeningocoele, or treatment failure during surgery. In this study, superiority over current practise practice (which included suture, duraplasty and fibrin and polymer sealants or combinations of these) could not be documented. The numbers of subjects experiencing an efficacy outcome event were 25 (6.9%) and 30 (8.2%) for TachoSil and current practice treated patients, respectively, providing an Odds Ratio of 0.82 (95% CI: 0.47, 1.43). However, the 95% confidence intervals for the odds ratio results indicated that TachoSil had similar efficacy to current practice. In this study two application techniques for TachoSil were evaluated: application of TachoSil over the dura and application of TachoSil on both sides of the dura. The results did not support the second method. TachoSil was found to be well tolerated and safe for use as an adjunct to dura mater closure in neurosurgery.

5.2. Pharmacokinetic properties

TachoSil is intended for epilesional use only. Intravascular administration is contraindicated.
Therefore, intravascular pharmacokinetic studies were not performed in man.

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

In animal studies, TachoSil biodegrades after administration to a wound surface with few remnants left after 13 weeks. Complete degradation of TachoSil was seen in some animals 12 months after its administration to a liver wound, whereas small remnants were still observed in others. The degradation was associated with infiltration of granulocytes and formation of resorptive granulation tissue encapsulating the degraded remnants of TachoSil. No evidence of local intolerability has been observed in animal studies.

From the experience in humans there have been isolated cases where remnants were observed as coincidental findings with no signs of functional impairment

5.3 Preclinical safety data

Single dose toxicity studies in different species of animals have shown no signs of acute toxic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin
L-Arginin-hydrochloride.
Collagen
Sodium Chloride
Sodium Citrate
Riboflavine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Once the foil sachet is opened, Tachosil must be used immediately.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Each sealant matrix 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 included and packed in a folding carton.
Pack sizes:
Package with 1 matrix of 9.5 cm x 4.8 cm
Package with 2 matrix of 4.8 cm x 4.8 cm
Package with 1 matrix of 3.0 cm x 2.5 cm
Package with 5 matrix of 3.0 cm x 2.5 cm

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

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. TachoSil should be used immediately after opening the inner sterile cover.

TachoSil is used under sterile conditions. Prior to application the wound area should be cleansed, e.g. from blood, disinfectants and other fluids. After removal of conventional, flat TachoSil from the sterile package it should be pre-moistened in saline solution and then applied immediately. The yellow, active side of the matrix is applied to the bleeding/leaking 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.

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, gloves or adjacent tissues covered with blood. This can be avoided by cleansing surgical instruments, and gloves and adjacent tissues before application. It is important to note that failure to adequately clean adjacent tissues may cause adhesions (see section 4.4). After pressing TachoSil to the wound, the glove or the pad must be removed carefully. To avoid TachoSil 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 3-5 minutes.

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

In neurosurgery, TachoSil should be applied on top of the primary dura closure.

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

7. MANUFACTURER

Takeda Austria GmbH
St. Peter Strasse 25, A-4020 Linz.
Austria

8. LICENSE HOLDER/ IMPORTER

CTS Ltd, Haharash 4, Hod - Hasharon

The content of this leaflet was approved by the Ministry of Health in February 2017 and updated according to the guidelines of the Ministry of Health in February 2020.