Leaflet	Graphic Design beginning - 01.10.2021 Aariya Regulatory Services Pvt. Ltd. - 15.11.2021 (R-1)					
Product name	TachoSil LFT SGP				Reason of change:	New Artwork
	6102081 / 2104 (6) / Code 1978					
Printed colours	Black				prev. version:	Not Applicable
Not printed colours		dye cut	Perforation: ()	Font sizes	product name: 14 pt text: 9 pt other: 6 pt	
Dimensions	420 x 297 mm					

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 homodimer,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

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

TachoSil contains fibrinogen and thrombin as a dried coating on the surface of an equine collagen sponge matrix. Following 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 to form 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 epilesional use only.

Fibrin sealants/hemostatics 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.

CLINICAL TRIALS

The haemostatic efficacy and safety of TachoSil was evaluated in four open-label, multicentre, 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 nonanatomical) 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 lifethreatening thromboembolic events.

PRECAUTIONS
General
TachoSil is for topical use only. There are no data on repeated application.
Do not use intravascularly. Thromboembolic complications may occur if the preparation is applied intravascularly.
Specific data have not been obtained on the use of this product in neurosurgery after recent radiation therapy or in gastrointestinal anastomic 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 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.

To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before administration of human fibrinogen/human thrombin sealant matrix (see 'Instructions for Use/Handling'). 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.

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 the Health Authority under Adverse Event Reporting.

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. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development Therefore, TachoSil should be administered to pregnant women only if the anticipated benefits outweigh the risks.

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 the anticipated benefits outweigh the risks.

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. An assessment of the carcinogenic potential of TachoSil was completed and demonstrated negligible carcinogenic risk from product use.

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 of TachoSil.

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.

Immunogenicity

Antibodies against components of fibrin sealant/hemostatic products may occur rarely.

However in a clinical trial with TachoSil in hepatic surgery 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 with unknown antibody status to collagen or fibrinogen have been re-exposed in a clinical trial and have not reported any immune-mediated adverse events.

Postmarketing

Following is a list of ADRs which have been observed in postmarketing and are not included above:

Immune system disorders: Anaphylactic shock, hypersensitivity

Vascular disorders: Thrombosis

Gastrointestinal disorders: Intestinal obstruction (in abdominal surgeries), ileus (in abdominal surgeries)

General disorders and administration site conditions: Adhesions

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 determined by the underlying clinical need for the patient. The number of TachoSil sponges to be applied vary and should be appropriate to the size of the wound area.

Application of TachoSil must be patient-specific and accordingly determined 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.

Instructions for use/handling
Preparation for Application:

- TachoSil comes ready to use in sterile packages and must be handled using sterile technique in aseptic conditions. Open or damaged packages should be discarded as resterilization is not possible.
- When in the operating room, the outer aluminium foil pouch may be opened in a non-sterile environment. The inner sterile blister must be opened in a sterile environment. TachoSil should be used immediately after opening the inner sterile cover.
- Remove TachoSil from the blister, which can be used as a container for pre-moistening of the sponge (patch), if needed. Determine the size of sponge(s) (patch (es) to be applied to the bleeding surface. Select the appropriate TachoSil so that it extends 1 - 2 cm beyond the margins of the wound. The sponge (patch) can be cut to the correct size and shape if desired. If more than one sponge (patch) is used, overlap sponges (patches) by at least 1 cm.
- Prior to application, cleanse the area to be treated to remove 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.
- Apply TachoSil directly to the bleeding area either wet or dry. If applied wet, pre-moisten TachoSil in 0.9% saline solution for no more than 1 minute and then apply immediately. In the case of a wet tissue surface (e.g., oozing or bleeding) TachoSil may be applied without pre-moistening.
- Use only undamaged packages.

Method of Application

- Cleanse surgical instruments, gloves and adjacent tissues with saline solution to reduce the adherence to TachoSil. The white, inactive side of TachoSil may also adhere to surgical instruments (e.g., forceps), gloves or adjacent tissues covered with blood due to the affinity of collagen to blood. It is important to note that failure to adequately clean adjacent tissues may cause adhesions (see 'Precautions').
- Apply the yellow, active side of the sponge (patch) to the bleeding area and hold in place with gentle pressure applied through moistened gloves or a moist pad for at least 3 minutes.
- To avoid pulling the patch loose, first place a clean surgical instrument at one end of the patch before relieving the pressure. Gentle irrigation may also aid in removing the premoistened pad or glove without removing TachoSil from the bleeding area.
- Leave TachoSil in place once it adheres to organ tissue. Only remove any unattached TachoSil or part of sponges (patches) and replace with new sponges (patches).
- TachoSil cannot be re-sterilized once removed from inner pouch. Discard unused, opened packages of human fibrinogen/human thrombin sponge (patch) at the end of the procedure.
- Record patient name and TachoSil batch number every time that TachoSil is administered to a patient.

Retreatment

If not satisfied with the placement of the sponge (patch), or if bleeding still occurs during or after the specified duration of compression, then repeat the application procedure as described above. Do not remove already applied and attached (partial) TachoSil.

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

OVERDOSAGE
No case of overdose has been reported.

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 centimeter 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
All pack sizes may not be marketed.

Store below 25°C.

Shelf Life: 36 months

PRODUCT REGISTRANT
PharmEng Technology Pte. Ltd.
1 Fusionopolis Place, #03-20 Galaxis
Singapore 138522

DATE OF LAST REVISION OF TEXT

6 October 2021

6102081
2104 ⑥
Code 1978