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 dihydrate 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.

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. 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 (see ‘Adverse Effects’).

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. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. 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. 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).

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 Takeda.

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

The safety of TachoSil for use in breastfeeding has not been established in controlled clinical trials. 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%)
Anaemia	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%)

Adverse Event (Preferred Term)	TachoSil N = 521				Comparator N = 511			
	Mild	Moderate	Severe	Any	Mild	Moderate	Severe	Any
Hyperglycaemia	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/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, about 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 to 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.

Postmarketing Experience

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 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.

Select the appropriate TachoSil size 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.

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. It is important to note that failure to adequately clean adjacent tissues may cause adhesions, see 'PRECAUTIONS'. 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.
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, gloves or adjacent tissues covered with blood. This can be avoided by pre-moistening surgical instruments, gloves and adjacent tissues 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.

Any unused, opened 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

Not all presentations may be marketed.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000

Distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie NSW 2146
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE ARTG 22 March 2012

DATE OF MOST RECENT AMENDMENT 4 May 2017