HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 December 2009

TACHOSIL medicated sponge
Pack of 1 sponge 9.5 cm x 4.8 cm (CIP: 565 807-5)
Pack of 1 sponge 3.0 cm x 2.5 cm (CIP: 565 809-8)
Pack of 2 sponges 4.8 cm x 4.8 cm (CIP: 565 808-1)
Pack of 5 sponges 3.0 cm x 2.5 cm (CIP: 565 810-6)

Applicant : NYCOMED

Equine collagen sponge coated with human thrombin and human fibrinogen stabilised with albumin

ATC Code: B02BC

List I - For hospital use only

MA dates (centralised procedure): June 8, 2004, February 28, 2006, February 10, 2009 (indications to be evaluated), April 30, 2009.

Reason for request: inclusion on the list of medicines approved for use by hospitals in the indication extensions “to promote tissue sealing, and for suture support in vascular surgery”.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Equine collagen sponge coated with human thrombin and human fibrinogen stabilised with albumin

1.2. Indications

"TACHOSIL is indicated in adults for supportive treatment in surgery to improve haemostasis where standard techniques are insufficient, **to promote tissue sealing, and for suture support in vascular surgery** ."

1.3. Dosage

The use of TachoSil is restricted to experienced surgeons.

The number of TachoSil sponges to be applied should always be oriented towards the underlying clinical need for the patient. The number of TachoSil sponges 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 sponges (9.5 cm x 4.8 cm); application of up to 7 sponges has been reported. For smaller wounds, e.g. in minimal invasive surgery the smaller size sponges (4.8 cm x 4.8 cm or 3.0 cm x 2.5 cm) are recommended.

Method and route of administration

For local use only. Do not use intravascularly.
See section 6.6 of SPC 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.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

B : blood and blood forming organs
B02 : antihemorrhagics
B02B : vitamin K and other hemostatics
B02BC : local hemostatics

2.2. Medicines in the same therapeutic category

Comparator medicines
TACHOSIL is the only thrombin and fibrin-based sponge for haemostatic use in surgery.

2.3. Medicines with a similar therapeutic aim

Fibrin glues indicated to facilitate tissue sealing and/or for suture support in vascular surgery:
BERIPLAST powders and solvents for sealant
Supportive treatment for local use in all surgeries where standard surgical techniques are insufficient:
-For improvement of haemostasis (including endoscopic treatment of bleeding gastroduodenal ulcer)
-As a tissue to promote adhesion/sealing or as suture support
EVICEL solution for sealant
Supportive treatment in surgery to improve haemostasis where standard surgical techniques are insufficient, for improvement of haemostasis (see SPC section 5.1). EVICEL is also indicated as suture support for haemostasis in vascular surgery.

It should be noted that two other fibrin glues are indicated for supportive treatment in surgery to improve haemostasis:
QUIXIL solutions for sealant
Supportive treatment in surgery to improve haemostasis when conventional techniques are insufficient.
Its efficacy has been demonstrated in hepatic and orthopaedic surgery (see SPC section 5.1).
TISSUCOL KIT powders, solution and solvent for intralesional sealant
Supportive treatment to facilitate local haemostasis during surgery.

Non-medicated treatments carrying the status of medical device are available.

3 ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of TACHOSIL compared to standard treatment is principally based on two randomised open-label studies:

- study TC-021-IM: pulmonary lobectomy for malignant lung tumour,
- study TC-023-IM: in cardiovascular surgery requiring heart-lung bypass.

3.1. Efficacy

Study TC-021-IM

Randomised open-label study evaluating the efficacy of TACHOSIL in comparison to an additional conventional method in second-line treatment of air leaks during surgery despite primary stapling in adults undergoing a pulmonary lobectomy due to lung cancer, with or without metastases.

Inclusion criteria:

- patients aged over 18,
- scheduled lobectomy due to lung cancer, with lymphadenectomy,
- grade 1 or 2 air leaks[1] after primary stapling and limited suturing if deemed necessary by the surgeon. Patients with grade 3 air leaks could be eligible after additional stapling and/or suturing.

Treatments:

- TACHOSIL group: as many TACHOSIL 9.5 x 4.8 cm sponges as necessary applied with pressure for 3 minutes (n=148),
- additional conventional method group: suturing, stapling or no additional initiative according to the usual procedures (n=151).

Primary endpoint: duration of postoperative air leaks (ITT)
The air leaks were evaluated on the evening of the surgery then daily, mornings and evenings.

Secondary endpoints:

- decrease in the intensity of air leaks during surgery after the first application of the treatment studied,
- time until first drain was removed,
- postoperative complications (particularly pneumonia, further surgery, redraining, assisted breathing, transfusions, etc.)

Results:

The patient characteristics and the surgical procedures were generally comparable in the 2 groups.
During randomisation, around one half of patients had grade 1 air leaks (52% of patients in the TACHOSIL group and 47% of those in the conventional method group).
The average duration of surgery was 144 minutes for patients treated with TACHOSIL and 142 minutes for those treated with the conventional method.
Of the 151 patients in the conventional method group, the additional conventional methods were suturing for 79 patients (53%), stapling for 23 (15%), another treatment for 4 patients (3%) and 42 patients (28%) had no further treatment after randomisation.

[1] grading of air leaks: grade 0 = no leak, grade 1 = air bubbles that can be counted, grade 2 = streams of bubbles, grade 3 = coalescing bubbles

- Primary endpoint:

The duration of postoperative air leaks (primary endpoint) was significantly less in the TACHOSIL group than in the conventional method group (p of log-rank test= 0.03).
The percentage of patients without an air leak was higher in the TACHOSIL group than the conventional method group in all evaluations (see table 1).

Table 1: Percentage of patients with air leaks (study TC-021-IM)

% of patients	D0: evening of surgery	D1: morning	D1: evening	D2: evening	D5: morning	D10: morning	D20: morning
TACHOSIL N=148	67	53	47	27	8	4	2
Conventional method N=151	73	59	49	31	17	8	2

- Secondary endpoints:

A decrease of at least 1 point in the score for intensity of air leaks during surgery was observed for 71% of TACHOSIL patients and 62% of conventional method patients (p=0.04).

The time until the chest drain was removed did not differ between the 2 groups (4.9 days in the TACHOSIL group and 5.5 days in the conventional method group).

The mean hospitalisation time was similar in both groups (9.3 days for TACHOSIL and 9.7 days for the conventional method group).

Postoperative complications were observed in 26% of patients treated with TACHOSIL (n=39) and 33% of those treated with a conventional method (n=50). The most common complications were cardiac arrhythmia, atelectasis and pneumonia.

An additional procedure was required for 11% of patients in the TACHOSIL group and the conventional method group: blood transfusion (4.7% vs. 6%), additional chest drain (4.7% vs. 4%), respiratory aid (2.7% vs. 2%) and a further operation (4% vs. 3.3%).
Between 30 and 38% of patients had a pneumothorax on D1 and before the drain was removed.

Study TC-023-IM[2]

Randomised, open-label study evaluating the efficacy of TACHOSIL compared to standard management in 119 patients aged over 18 undergoing cardiovascular surgery.

Inclusion criteria:

- scheduled cardiovascular surgery on the heart, ascending aorta or arch of aorta requiring heart-lung bypass;
- bleeding in the heart muscle, pericardium, a major blood vessel or the vascular bed requiring haemostatic treatment, the location of which was able to be identified and accessed for compression with TACHOSIL.

Exclusion criteria:

- known coagulation problems,
- disseminated intravascular coagulation (at randomisation),
- patients having received a fibrin glue (at randomisation).

Treatments: after initial haemostatic treatment has failed

- TACHOSIL group: as many TACHOSIL sponges as necessary applied by pressure for 3 minutes,
- additional conventional method group: any other haemostatic device not comprising an active coagulation factor, applied by pressure for 3 minutes.

If haemostasis was not achieved after 3 minutes, the treatment was reapplied for 3 minutes. Sutures were not allowed.
If treatment failed, rescue treatment was initiated.

Primary endpoint: percentage of patients for which haemostasis was achieved after 3 minutes.

Secondary endpoints:

- percentage of patients for which haemostasis was achieved after 6 minutes,
- incidence of further surgery for bleeding,
- postoperative transfusions,
- draining duration (hours) and volume.

Results:

Patient characteristics were similar in the 2 groups.
The first-line haemostatic treatment applied did not differ in the 2 groups: sutures (72%), no treatment (18.5%), electrocoagulation (9%), clip (4%) or gauze (1%).
The mean duration of surgery was 249 minutes in the TACHOSIL group and 235 minutes in the conventional method group.
There was no major difference in surgical characteristics in the 2 groups (see table 2).
The principal area of bleeding was the aorta (56%). The bleeding came from a vascular suture in 68% of patients (TACHOSIL: 73%; conventional method: 63%). The bleeding was mostly slight to moderate and arterial (TACHOSIL: 81%; conventional method: 67%).

[2] Maisano F, Kjaergard HK et al. TachoSil surgical patch versus conventional haemostatic fleece material for control of bleeding in cardiovascular surgery: a randomised controlled trial. European Journal of Cardio-thoracic Surgery 2009 Oct ; 36(4):708-14

Table 2: Main surgical patient characteristics (study TC-023-IM)

% of patients	**TACHOSIL** N=59	**CONVENTIONAL METHOD** N=60	**TOTAL** N=119
Area treated			
Aorta	59	53	56
Right ventricle	19	13	16
Right atrium	9	17	13
Origin of bleeding			
Vessel	73	63	68
Tissue	27	37	32
Type of bleeding			
Arterial	81	67	74
Venous	19	33	26
Intensity of bleeding			
Slight	32	40	36
Moderate	59	57	58
Severe	9	3	6

In the TACHOSIL group, 1.2 sponges were used per patient on average.
In the conventional method group, 28 patients were treated by compression and gauze (49%), 24 by compression and haemostatic fibrillar absorbable gauze (42%), 4 with suturing (7%) and 1 with TISSUCOL (2%).

- Primary endpoint:

The percentage of patients in which haemostasis was achieved after 3 minutes was 74.6% (95%CI 64% - 86%) in the TACHOSIL group and 33.3% (95%CI 21% - 45%) in the conventional method group ($p<0.0001$). Similar results were observed in the PP population.

- Secondary endpoints:

The percentage of patients in which haemostasis was achieved after 6 minutes was 95% in the TACHOSIL group and 72% in the conventional method group ($p<0.001$).

The median duration of draining was similar in both groups (46 hours in the TACHOSIL group and 44 hours in the conventional method group).
The median postoperative draining volume was 600 ml in the TACHOSIL group and 498 ml in the conventional method group.

In postoperative treatment, 26 patients treated with TACHOSIL (42%) had 51 blood transfusions and 22 patients in the conventional method group (39%) had 44 transfusions.

Failed treatments requiring rescue treatment were observed in 3 patients in the TACHOSIL group (5%) and 17 patients in the conventional method group (28%).

The mean hospitalisation time was 11.4 days in the TACHOSIL group and 13.8 days in the conventional method group.

Further surgery was necessary for three TACHOSIL patients (5%) and 8 conventional method patients (14%); this surgery was not connected to the study treatment.

Another postoperative complication was observed in 27 patients treated with TACHOSIL (44%) and 31 patients treated with the conventional method (54%).

3.2. Safety

Study TC-021-IM

In each group, 66 patients had at least one severe adverse event (44%).
In the TACHOSIL and conventional method groups, the most frequent adverse events were: pneumonia (10 in each), atelectasis (7 vs. 10), atrial fibrillation (11 vs. 5), constipation (5 vs. 9), bronchopleural fistula (4 vs. 10), flatulence (2 vs. 7), fever (6 vs. 3), pneumothorax (4 vs. 5), pleural effusion (5 vs. 2), anaemia (3 vs. 4).

Study TC-023-IM

In the TACHOSIL group, 149 adverse effects were reported for 46 patients (74%) and in the conventional method group, 179 adverse events were observed for 44 patients (77%).
In the TACHOSIL and conventional method groups, the most frequent adverse events were: supraventricular arrhythmia (20 vs. 16), pleural effusion (14 in each), nausea (8 vs. 5), hyperglycaemia (6 vs. 7), anaemia induced by bleeding (5 vs. 6).

Potential risks of fibrin-based haemostatics (SPC data)
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.

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

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

For viral safety see section 4.4

Pharmacovigilance data 2004 to June 2008

Over this period, over 830,000 sponges were sold (i.e. approximately 415,000 patients exposed). No new concern has been identified.

An observational cohort study (TC-018-IN) served to evaluate the safety, particularly thromboembolic and immunological events and drug interactions causing major postoperative bleeding and thromboembolic events. The aim of this study was to obtain systematic safety data under the conditions of use of TACHOSIL.

According to the CHMP's findings adopted on September 25, 2008, the data analysed, covering 3,600 patients, did not identify thromboembolic and immunological or haemorrhagic events linked to TACHOSIL or to drug interactions.

3.3. Conclusion

The efficacy and safety of TACHOSIL in promoting tissue sealing and for suture support were evaluated in two randomised, open-label studies in pulmonary and cardiovascular surgery in adults.

In patients undergoing a pulmonary lobectomy and where there was an air leak during surgery despite conventional treatment, the duration of postoperative air leaks (primary endpoint) was significantly less in the TACHOSIL group than in the conventional method group (p of log-rank test= 0.03).

The type and frequency of postoperative complications, additional procedures, number of transfusions and length of hospitalisation were generally similar in the two groups.

In scheduled cardiovascular surgery on the heart, ascending aorta or arch of aorta requiring a heart-lung bypass, the percentage of patients in which haemostasis was achieved after 3 minutes (primary endpoint) was 74.6% (95%CI 64% - 86%) in the TACHOSIL group and 33.3% (95%CI 21% - 45%) in the conventional method group ($p<0.0001$).

Overall, neither study raised new concerns for safety. In general, the adverse events were similar in the treatment groups and connected to the underlying conditions or co-morbidities and/or surgical procedures.

The data is too limited to support the efficacy and safety of TACHOSIL in children.

There is no study comparing TACHOSIL to another treatment adjuvant to conventional haemostasis methods.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions covered by the indication extension of TACHOSIL (promoting tissue sealing and for suture support in vascular surgery) can be fatal.

The efficacy of this supportive treatment has been demonstrated in pulmonary surgery and cardiovascular surgery. The efficacy/adverse effects ratio is high.

The product is intended for supportive curative treatment.

It is a second-line treatment to promote tissue sealing where standard techniques are insufficient, and for suture support in vascular surgery.

Public health benefit:

Bleeding is a major factor in postoperative complications and mortality in surgery. Supportive haemostatic treatment does not concern major bleeding. The public health burden of bleeding that can be treated with supportive haemostatic treatment can be considered low.
TACHOSIL could help to reduce postoperative morbidity similarly to other supportive haemostatic treatments.
However, in light of available data [the success of haemostasis at a given time and decrease in the duration of air leaks but with no effect on postoperative complications (particularly draining duration and length of hospitalisation)], and in the absence of data comparing with another supportive treatment, the impact of TACHOSIL in terms of morbidity and mortality has yet to be demonstrated.
Furthermore, the clinical result also depends on the type of surgery and on how well the surgeon masters the surgical technique.
Consequently, TACHOSIL is not expected to have an impact on public health.

There are alternative medicinal and non-medicinal treatments.

The actual benefit is substantial.

4.2. Improvement in actual clinical benefit

TACHOSIL does not provide any improvement in actual benefit (IAB V) compared to other supportive treatments to promote tissue sealing and for suture support in vascular surgery, where standard techniques are insufficient . Indeed, although TACHOSIL reduces the duration of postoperative air leaks in pulmonary surgery and increases the success rate of haemostasis in cardiovascular surgery compared to conventional methods alone, it does not change postoperative complications and there is no comparison with another treatment adjuvant to conventional methods.
However, the committee feels that TACHOSIL is a useful additional means of treatment.

4.3. Therapeutic use

The aim of haemostatic treatments during surgical procedures is to achieve rapid healing, limit blood loss and the risk of postoperative complications and to reduce the need for transfusion.

The quality of the haemostasis and the tissue binding is primarily influenced by the surgical technique and how well the surgeon masters the latter.

In addition to the conventional haemostasis methods, an adjuvant treatment can be necessary, particularly in rescue situations.

The type of haemostatic agent used depends on the type of surgery, its location, the type of bleeding and the surgeon's experience.

In the indication extensions, TACHOSIL is indicated as an adjuvant treatment where standard techniques are insufficient in surgeries requiring additional tissue sealing, particularly in pulmonary surgery to treat postoperative air leaks and to support sutures for haemostasis in vascular surgery.

The efficacy of TACHOSIL in the treatment of air leaks during surgery despite primary stapling was demonstrated in a randomised open-label study on adults undergoing a pulmonary lobectomy due to lung cancer.
The meta-analysis by Serra-Mitjans M et al.[3] evaluated the efficacy of surgical glues (fibrin glues and medical devices) in preventing or reducing air leaks after pulmonary resections due to lung cancer. In light of the data available, the authors conclude that these results do not enable systematic use of surgical glues to be recommended in practice.
According to experts, TACHOSIL could be used when pulmonary tissue is particularly fragile, which limits stapling and clamping techniques or makes them impossible, i.e. in patients with advanced fibrosis or emphysema, chronic obstructive pulmonary disease, pulmonary decortication or parenchymal tearing.

The efficacy of TACHOSIL for suture support has been demonstrated in scheduled cardiovascular surgery on the heart, ascending aorta, or arch of aorta requiring a heart-lung bypass after initial haemostatic treatment has failed.

In light of the available data and the absence of comparison with an adjuvant treatment, TACHOSIL is an alternative to other surgical haemostatic agents in promoting tissue sealing and for suture support in vascular surgery, where standard techniques are insufficient, excluding neurosurgery, gastrointestinal anastomosis and application by use of a flexible endoscope for the treatment of bleeding for which specific data is awaited.

[3] Serra-Mitjans et al. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer (Review) The Cochrane collaboration, Issue 3, 2005

4.4. Target population

The population corresponding to the use of TACHOSIL in the indication extensions is comprised of patients benefiting from:

- surgery requiring additional tissue sealing when standard techniques (suturing, stapling, etc.) are insufficient (e.g. pulmonary surgery),
- cardiovascular surgery requiring suture support for haemostasis.

The data is too limited to support the efficacy and safety of TACHOSIL in children. There is no sufficiently relevant data to support the use of TACHOSIL in neurosurgery, by use of a flexible endoscope for the treatment of gastrointestinal anastomosis or bleeds.

There is no data in literature on the number of bleeds or air leaks requiring additional haemostasis or binding for any given surgical procedure. It is therefore difficult to specify the number of patients able to benefit from TACHOSIL for each type of surgery.

TACHOSIL is to be used only by experienced surgeons.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the MA indication extensions and dosages.

The committee stresses that it is likely to reevaluate TACHOSIL according to the findings of the review of surgical haemostatic agents.