Scottish Medicines Consortium

TachoSil® No. (168/05)

Nycomed

8 April 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and ADTCs on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

TachoSil® is accepted for use within NHS Scotland for the improvement of haemostasis in liver surgery where standard techniques are insufficient.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

TachoSil®

Licensed indication under review

TachoSil® is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. Efficacy has only been demonstrated in liver surgery. The use of TachoSil® is restricted to experienced surgeons.

Dosing information under review

The number of sponges applied is governed by the size of the wound area. Application must be individualised by the treating surgeon. In clinical trials the individual doses have typically ranged from 1-3 sponges (9.5cm x 4.8cm).

UK launch date

9.5cm x 4.8cm x 0.5cm September 2004
4.8cm x 4.8cm x 0.5cm anticipated 2005

Comparators

Quixil® Human Surgical Sealant, FloSeal® Matrix Haemostatic Sealant, Argon beamer

Cost per treatment period and relevant comparators

	No of applications	Cost per operation
TachoSil® medicated sponge	**1-3 sponges**	**£190-£570**
FloSeal ™ Matrix	5ml	£146
Quixil™ Human Surgical Sealant	5-10ml	£361-£721

Prices quoted are from the companies' list price.

Summary of evidence on comparative efficacy

Surgical supportive treatments are used to control wound bleeding and support tissue integrity when standard surgical techniques such as suturing, stapling and ligation are ineffective. Supportive treatments include argon beamer, which uses heat energy to cauterise the wound, and liquid haemostatic sealants. TachoSil® consists of a collagen sponge coated with human fibrinogen and thrombin. On contact with physiological fluids, the coagulation factors dissolve, initiating the last phase of physiological blood coagulation. The formation of a fibrin clot brings about haemostasis, making the collagen adhere tightly to the wound and providing wound sealing.

Two multi-centre, open, randomised phase lll trials of similar design and in a total of 240 patients, compared TachoSil® with argon beamer in elective liver surgery. The primary endpoint in both trials was time to haemostasis with secondary endpoints of percentage of subjects with haemostasis at 10 minutes, volume and haemoglobin concentration of drainage fluid at 24hr and 48hr post-surgery and total volume and duration of fluid drainage. The follow up period was one month. In the first trial, after liver resection and primary haemostatic treatment, 121 patients with persistent minor or moderate haemorrhage were randomised to either TachoSil® (n=59) or argon beamer (n=62). Haemostasis was judged to have been achieved when there was no visible bleeding from the target site. The median time to haemostasis in the TachoSil® group was 3.0 minutes, range 3-20 min (mean 3.9 ± 2.8 min) and 4.0 minutes, range 3-39 min (mean 6.3 ± 6.2 min) in the argon beamer group (p=0.0007). The estimated ratio of mean time to haemostasis for TachoSil® relative to argon beamer was

0.38 (95% CI: 0.22-0.68, p=0.0009). There was no significant difference between treatments in the proportion of patients with haemostasis at 10 minutes or the volume of drainage at 24 and 48 hours post-surgery. The haemoglobin concentration of the drainage fluid was significantly lower with TachoSil® at 48 hours (p=0.012) but not at 24 hours. The mean duration of drainage was significantly shorter in the argon beamer group (5.7 vs. 8.2 days, p=0.005), although median duration was comparable (5.1 days vs 6.0 days for argon beamer and TachoSil®). There were reservations about the robustness of the results from this trial due to mixed results for the secondary endpoints, the baseline differences between treatment groups (mean area of the wound, 84cm^2 vs 65cm^2, the number of patients undergoing more than 4 resections, 10 vs 4 patients for TachoSil® and argon beamer, respectively) and the premature stopping of the open trial due to slow recruitment. Therefore a second trial with tighter internal controls was undertaken in 119 patients undergoing elective liver resection. The mean number of resected segments and the median area of the target wound were lower in the TachoSil group than for argon beamer (2.7 vs 3.2 resected segments and 47.1cm^2 vs 63.4cm^2, respectively). The median time to haemostasis was 3.0 minutes, range 3-8 min (mean 3.6 ± 0.9min) in the TachoSil® group (n=60) and 3.0 minutes, range 3-23 min (mean 5.0 ± 3.6min) in the argon beamer group (p=0.0018). The estimated ratio of mean time to haemostasis for TachoSil® relative to argon beamer was 0.61 (95% CI: 0.47-0.80, p=0.0003). There was no difference between the groups in the secondary endpoint outcomes.

TachoSil® was preceded to market by two similar products which mainly differed from TachoSil® in the human and bovine origin of the constituents. The company submitted trials from these products as supportive evidence. In a trial of 292 patients undergoing liver resection and comparing argon beamer, observation and TachoComb H® (which differs from TachoSil® in the presence of bovine aprotinin), the primary and secondary outcomes supported those reported in the two trials described previously. The two trials of TachoComb® (which contains bovine aprotinin and thrombin) were comparisons against two different fibrin sealants neither of which are licensed in the UK.

Summary of evidence on comparative safety

The adverse events were equally distributed between treatment groups. In the first trial described in the efficacy section, one adverse event was experienced by 26 patients receiving TachoSil® and 24 patients receiving argon beamer. The most common adverse events were abscess formation (8.5% vs 4.9%, TachoSil® vs argon beamer), fever (5.1% vs 6.6%), gall bladder disorder (6.8% vs 3.3%), pneumonia (3.4% vs 6.6%) and postoperative wound infection (6.8% vs 3.3%). In the second trial, 25 TachoSil® patients and 28 argon beamer patients experienced 47 and 45 adverse events, respectively, with the most frequently reported including myocardial infarction (8.3% vs 0%, TachoSil® vs argon beamer), urinary tract infection (3.3% vs 1.7%), ascites (3.3% vs 1.7%), wound infection (1.7% vs 3.3%), pneumonia (5.0% vs 0%), pleural effusion (5.0% vs 0%) and pulmonary failure (5% vs 0%). Twenty-three serious adverse events were reported in 14 TachoSil patients ® in the first trial, but only one event, post-operative haemorrhage, was thought to be related to treatment. In the second trial, 14 serious adverse events were reported in 10 TachoSil® patients, two of these were considered possibly related to the treatment, post-operative abscess and liver abscess. Eight deaths were reported in total in the first trial, six in the TachoSil® group and two in the argon beamer group and, six deaths in total in the second trial, two in the TachoSil® group and four in the argon beamer group. None of the deaths were considered by the investigators to be related to Tachosil®. The number of deaths in each group in the two trials may reflect the variation in the baseline characteristics of the patients in the different arms. However, the EPAR concluded that a contribution from the test agent to the six deaths in the first study described could not be confidently excluded and found it not possible to evaluate whether

some or all of these deaths had an element of thrombotic complication. The company has a post-marketing commitment to undertake a prospective safety monitoring study with particular focus on thromboembolic events, immunological reactions and potential interactions.

Summary of clinical effectiveness issues

Although the evidence and the subsequent post-marketing experience with the predecessors of TachoSil®, TachoComb® and TachoComb H®, is fairly extensive, the evidence base for TachoSil® itself is at present fairly limited. The comparator in the two trials was argon beamer against which it achieved significantly better time to haemostasis but no difference in the post-operative secondary outcomes. However, the company have stated that they do not anticipate TachoSil® will replace argon beamer but other fibrin sealants. However, no trials have been undertaken comparing TachoSil® with other sealants and although two trials were submitted comparing TachoComb® with two fibrin sealants, neither of these sealants are licensed for use in liver surgery in the UK. There is no indication from the company that trials against other sealants are planned. For Quixil® and FloSeal®, the two sealants licensed for use in liver surgery in the UK, there is no published evidence available in liver surgery other than a briefly reported trial in the Quixil® marketing literature. Published trials are available for FloSeal® in cardiac and vascular surgery. Therefore to make even an indirect comparison between the sealants is difficult. The one practical advantage of TachoSil® over the other two sealants is that it requires no special storage requirements and no preparation before use other than moistening with saline. Additionally its presentation as a collagen sponge may facilitate application of pressure to a bleeding site while haemostasis is being achieved.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing TachoSil® to a weighted average of FloSeal® and Quixil® (based on their market shares in Scotland). This predicts that TachoSil® has a net cost saving so long as no more than two large and one medium-sized sponges are required.

The clinical evidence for assuming that the three products have equal effectiveness is weak as there are no head-to-head trials and the indirect comparison did not establish that the patient groups and trial protocols were comparable.

The cost analysis was based on an assumption that current practice involved the use of 5ml kits of Quixil® and FloSeal®; in fact, smaller doses of Quixil® are available at a lower price. In addition, the weighted average cost of the two products used was based on their current market share, not highlighting that 5ml of FloSeal® is only slightly more expensive than one medium-sized TachoSil® sponge.

The analysis depended on the concept of “incremental cumulative cost”. While TachoSil® may be cost saving for the smallest wounds, it is not cost saving for small-to-medium sized wounds. Thusfor wounds of medium size or greater, TachoSil® may cost more but in cumulative terms there is still an overall saving because it is cheaper for small wounds. When this is corrected for, TachoSil® is only cost saving when either a single medium or single large sponge is used. .

Budget Impact

The manufacturer estimates a net saving of £3k based on 69 patients being switched from Quixil® or FloSeal® to TachoSil®. This is probably an overestimate and the true saving is likely to be smaller.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including ***11 March 2005.***

Drug prices are those available at the time of SMC assessment.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

References

Nycomed, Data on file; Clinical study report TC-014-IN. 2002.

Nycomed, Data on file; Clinical study report TC-016-IN. 2003.

Nycomed, Data on file; Clinical study report PHTC-009. 1999

European Medicines Agency (EMEA), European Public Assessment Report for TachoSil http://www.emea.eu.int/humandocs/PDFs/EPAR/tachosil/028904en6.pdf.