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Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA  
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## Horizon Scanning Technology Prioritising Summaries

# Vivostat® System for perioperative preparation and application of autologous fibrin sealant

September 2006



**ASERNIPs**

**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**



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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat  
Department of Health and Ageing  
MDP 106  
GPO Box 9848  
Canberra ACT 2606  
AUSTRALIA

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This Horizon scanning prioritising summary was prepared by staff from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).



### Name of Technology:

Vivostat® system (Vivolution A/S, Denmark) for perioperative preparation and application of an autologous fibrin sealant.

### Purpose and Target Group:

The Vivostat system was designed to produce patient-derived fibrin sealant during an operative procedure as a means of maintaining haemostasis during various surgical procedures.

### Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Not yet emerged

The Vivostat system is currently not available in Australia. Hence it is not listed or registered in the Australian Register of Therapeutic Goods database.

### International Utilisation:

| COUNTRY       | LEVEL OF USE    |             |                 |
|---------------|-----------------|-------------|-----------------|
|               | Trials underway | Limited use | Widely diffused |
| United States | ✓               |             |                 |
| Europe        |                 | ✓           |                 |

### Impact Summary:

#### *Background*

Fibrin sealants are compounds utilised as haemostatic or adhesive agents during surgical procedures that have been increasingly used during the last few years. In practice, fibrin sealant is a two-component system, concentrated fibrinogen and factor XIII are combined with thrombin and coagulum, essentially emulating the final stages of the clotting cascade (Vivolution 2006).

In comparison to conventional haemostatic and adhesive techniques, fibrin sealants may offer advantages with regards to ease of use and clinical outcomes. However, despite the low rates of adverse events related to the use of fibrin sealants (Le Guehenec *et al.* 2004), there are certain risks associated with their use. Fibrin sealants are prepared from pooled



human plasma (fibrinogen, thrombin) and sometimes animal-derived components (e.g. bovine aprotinin or thrombin). As a result of this, fibrin sealants carry a potential risk of transmitting human or animal-borne infectious materials such as viruses (hepatitis B and C, human T-cell leukaemia, HIV) or prions (Bovine spongiform encephalopathy) (Belboul *et al.* 2004). Additional concerns include antigenic reactions to foreign proteins; previous studies have revealed a disconcerting trend for increased risks of anaphylactic shocks (up to 5%) in patients exposed to multiple applications of bovine-derived fibrin sealants between two weeks and six months after the first exposure (Spotnitz *et al.* 2004).

The obvious approach to address the concerns associated with the use of animal or human donor derived fibrin sealants is to utilise autologous fibrin sealants, fibrin sealants produced using thrombin and fibrinogen extracted from the patient's own blood. However the process of producing autologous fibrin sealants are often labour intensive and time consuming. The Vivostat system was designed to overcome the complexities and inconveniences of producing autologous fibrin sealants. It is a fully automated system designed for on-site preparation and application of patient-derived fibrin sealant (Vivostat fibrin sealant) and comprises three main components (Vivolution 2006):

- The processor unit which drives and controls the production of a concentrated fibrin I solution from the whole blood within a disposable preparation unit
- An applicator unit which controls the delivery of the fibrin sealant, it houses the fibrin I as well as buffer cartridges and it feeds the solutions to the application pen via a multilumen catheter
- A disposable single-use patient kit which contains all the required components to prepare and apply the fibrin sealant. Production of autologous fibrin sealant with the Vivostat system begins with the drawing of 120ml of blood into the preparation unit, which is then mixed with an anticoagulant. The preparation unit requires 23 minutes to produce the autologous fibrin I solution.

### ***Clinical Need and Burden of Disease***

Topical haemostatic agents are used regularly as a means of controlling capillary, venous and small arterial haemorrhages that occur during surgical procedures. Fibrin sealants in particular have become a valuable adjunct in surgical procedures to control bleeding and their use continues to increase as more efficient and safer fibrin sealants are developed. At the time of writing, the Vivostat system is the only system of its kind for on-site preparation of autologous fibrin sealant (Vivolution 2006).



### ***Estimated Speed and Geographic and Practitioner Use Patterns of Diffusion in the Health System***

The Vivostat system is currently being marketed in Europe and has been utilised in various surgical procedures. In the United States, the Vivostat system is currently undergoing clinical trials (Hanks *et al.* 2003). The purported ease of use of the Vivostat system may offer substantial benefit compared to conventional preparation of autologous fibrin sealants and therefore may be rapidly adopted in Australia, provided its safety and efficacy has been firmly established.

### ***Existing Comparators***

- Tisseel (Baxter Healthcare Inc.)
- Avitene (CR Bard Inc.)
- Gelfoam (Pharmacia & Upjohn Inc.)
- Oxycel (Parke-Davis)
- Surgicel (Ethicon Inc.)
- Surgicel Nu-Knit (Ethicon Inc.)
- Thrombin-JMI (King Pharmaceuticals Inc.)
- Crosseal (Omrix Biopharmaceuticals Inc.)
- All other surgical sealants used for achieving haemostasis or adhesion

### ***Estimated Cost Impact***

In the United States, Vivostat procedure kits (which include the transeptal cannula, pump, infusion assembly, syringe, holster and hollister patches) cost USD\$19,500. The controller unit costs USD\$50,000 if the hospital chooses to purchase it. Alternatively, Vivolution A/S can provide the controller unit on consignment. In Europe, controller units are rented to hospitals for EU\$1,000 per month with a one year commitment (personal communication, Vivolution representative 2006). It is unknown if the high initial costs of utilising Vivostat will be offset by its ease of use and potential safety compared to other fibrin sealants.



## ***Efficacy and Safety Issues***

### **List of Studies Found**

|                              |   |
|------------------------------|---|
| Total number of studies      | 8 |
| Randomised controlled trials | 4 |
| Case series studies          | 4 |

The studies included in this summary are highlighted in bold in the reference list. Four randomised controlled trials were selected to be included in this summary as they represent the highest level of evidence currently available on the safety and efficacy of Vivostat. Case series studies have been excluded due to the size limitations imposed on prioritising summaries.

### ***Safety***

One serious adverse event was documented by Kjaergard *et al.* (2000), whereby a patient was hospitalised after suffering from sternal wound infection and coliform septicaemia post-treatment after the application of Vivostat to achieve haemostasis of the sternal marrow. This patient eventually died due to renal and multiple organ failure. Vivostat could not be positively excluded from causing the initial sternal infection which afflicted the patient, but the authors believed that it was not associated with the use of Vivostat (Kjaergard *et al.* 2000). Drake and Wong (2003) reported two cases of serious adverse events which occurred in the same patient after treatment. The first event was excessive post-operative bleeding from the left leg which required oversewing of the arterial bleed. The second event was non-improving thrombophlebitis of the right forearm, which required surgery to explore and excise the area (Drake and Wong 2003).

In the Vivostat studies included in this summary, no adverse events related to the use of the autologous fibrin produced using the Vivostat system were recorded (Belboul *et al.* 2004, Drake and Wong 2003, Kjaergard *et al.* 2000, Hanks *et al.* 2003). With regards to device malfunctions, Drake and Wong (2003) encountered one problem in priming the applicator and several problems with regards to the collection and processing of blood, however only one of these was a result of device error whilst the rest were attributed to human error. Meanwhile, Hanks *et al.* (2003) documented one case where an equipment malfunction prevented the application of the Vivostat sealant.

### ***Efficacy***

The randomised controlled trial conducted by Belboul *et al.* (2004) evaluated the efficacy and safety of Vivostat as an adjunct to surgical repair for air leaks after pulmonary lobectomy. Patients were randomised to receive Vivostat (n = 20) or no additional treatment (n = 20) after surgical repair. The use of Vivostat as an adjunct resulted in a mean 255ml lower total drainage volume in the 24h postoperative period (Vivostat: 370 ± 103 ml vs Control: 525 ±



152 ml,  $p < 0.001$ ) as well as a mean 382 ml lower total drainage volume compared to controls (Vivostat:  $424 \pm 139$  ml vs Control:  $782 \pm 376$  ml,  $p < 0.001$ ). In addition to this, the Vivostat group had a significantly greater number of patients without air leak immediately after surgery (16/20 patients, 80%) compared to the control group (8/20 patients, 40%). However, four patients (4/16 patients, 25%) in the Vivostat group who did not have air leakage immediately post-surgery developed air leaks one day post-surgery, a markedly higher proportion compared to the control group (1/8 patients, 12.5%). Overall, the proportion of patients without air leakage at any time post-operatively favours the Vivostat recipients, with 12/20 (60%) of the Vivostat group compared to 7/20 (35%) of the control group ( $p = 0.01$ ). The Vivostat group recorded a significantly lower median air leak (differences in medians = 0.5 l/min,  $p = 0.01$ ) and this averaged over the period of chest tube drainage (differences in medians = 0.6 l/min). No significant differences were noted for median durations of chest-tube drainage and hospitalisation times between the two patient groups (Belboul *et al.* 2004). It is imperative to note that the decision of the authors to compare Vivostat with no treatment elevates the potential of bias in this study, which may have resulted in overestimation of Vivostat's benefit.

Drake and Wong (2003) compared the haemostatic efficacy of Vivostat to a commonly utilised haemostat thrombin solution to reduce bleeding of split-thickness skin graft donor sites. Patients ( $n = 34$ ) were randomised before receiving simultaneous applications of either patient-derived Vivostat sealant or thrombin solution to the upper or lower half of a single donor site, so each patient acted as their own control. Blinded observers were used to determine the efficacy outcomes and observation lasted for a maximum of 10 minutes. Vivostat-treated wounds achieved considerably lower mean ( $68 \pm 82$  seconds) and median (31 seconds, range: 5 to 398 seconds) times to haemostasis compared to wounds treated with the thrombin solution (mean:  $135 \pm 158$  seconds; 59 seconds, range: 22 to 601 seconds). Despite large variations in time to haemostasis between patients, the difference between treatments were significant with regards to median time to haemostasis ( $p = 0.0012$ ). Overall, 26/34 (76.5%) patients achieved lower time to haemostasis on the wound site treated with Vivostat compared to the site treated with thrombin, survival analysis revealed that there was a significantly greater probability of achieving haemostasis with Vivostat sealant compared to the thrombin solution at any time up to 10 minutes ( $p = 0.014$ ). All donor sites wounds appeared normal on inspection one week after the procedure (Drake and Wong 2003).

In the randomised trial by Hanks *et al.* (2003), Vivostat sealant ( $n = 35$ ) was compared with Surgicel (oxidised cellulose) ( $n = 34$ ), a commonly used and effective haemostatic material, in various surgical wounds to control bleeding. Patients undergoing cardiothoracic, obstetric/gynaecological, vascular or general surgery were included. The unblinded investigator judged the efficacy outcomes and success was defined as haemostasis within 5 minutes. Vivostat achieved a significantly shorter time to haemostasis overall (Vivostat:



mean  $\pm$  SD = 1.6  $\pm$  1.3 min, median = 1.3 min; Surgicel: mean  $\pm$  SD = 3.3  $\pm$  1.7 min, median = 3.2 min;  $p < 0.0001$ ) and in addition to this, Vivostat treatment was associated with greater treatment success as there were fewer failures to haemostasis within the 5 minute assessment time prior to additional intervention to stop bleeding (Vivostat: 5.7% failure, Surgicel: 35.3% failure,  $p = 0.003$ ). The chances of achieving successful haemostasis with Vivostat were significantly greater at all treatment times compared to Surgicel ( $p < 0.0001$ ). No significant correlation was noted between the time to haemostasis and wound size overall or within each of the treatment groups. As expected, there was a significant positive correlation between volume of haemostatic material used and the time to haemostasis ( $r^2 = 0.190$ ,  $p = 0.009$ ). Due to the fact that surgeons were free to utilise their discretion in determining the amount of Vivostat sealant to use, it was impossible to evaluate the inherent haemostatic properties of the materials themselves. The authors proposed that Vivostat may have a mode of action which involves both inactive mechanisms (physical presence) and active mechanisms (e.g. Activation of platelet and coagulation factors), thus providing a possible explanation for its results compared to Surgicel which only acts by physical means (Hanks *et al.* 2003).

Kjaergard *et al.* (2000) examined the feasibility of using Vivostat to halt bleeding from the sternal marrow after median sternotomy. Thirty patients were randomised to receive Vivostat either of the right or left side of the sternum, with the opposite site acting as a control (not treated with any special haemostatic agent). The average time to haemostasis was 43 seconds for the Vivostat treated side, while the control sites required 180 seconds to achieve haemostasis ( $p < 0.001$ ). Meanwhile, complete haemostasis was achieved in 24/30 (80.0%) sides treated with Vivostat, a significantly higher rate to 4/30 (13.3%) of the control sides ( $p < 0.001$ ). Some residual bleeding in small areas (1cm x 1cm) was identified in 6/30 (20%) of Vivostat treated sides (Kjaergard *et al.* 2000). However, despite the promising results presented by Kjaergard *et al.* (2000), the complete lack of treatment on the control side of the sternum raises considerable doubt as to whether it was the most suitable comparator.

### ***Ethical Issues***

No issues were identified from the retrieved material.

### ***Cultural or Religious Considerations***

There may be some issues arising from Jehovah Witnesses due to the fact blood must be extracted to produce the Vivostat fibrin sealant.

### ***Other Issues***

No issues were identified from the retrieved material.



## Recommendation

Based on the included studies (3 surgical studies, 1 burns study), the Vivostat system appears to be capable of producing relatively safe and effective autologous fibrin sealant perioperatively. Preliminary results indicate that the Vivostat sealant is more effective compared to an existing haemostatic agent (Surgicel) (Hanks *et al.* 2003). The overall results are highly supportive of Vivostat, however the lack of a suitable comparator in two of the included studies (Belboul *et al.* 2004, Kjaergard *et al.* 2000) highlights the need for further randomised comparative studies with existing haemostatic agents for an accurate depiction of Vivostat's effectiveness compared to existing treatments. Based on the evidence available, it is recommended that the following is conducted:

- |  |  |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor                 | <input checked="" type="checkbox"/> Archive                |

## References:

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### Search Criteria:

A search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the UK National Research Register, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted in July 2006.

Search terms used were: 'Vivostat', 'Autologous fibrin sealant', 'Autologous fibrin glue', 'patient derived sealant'.



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This Horizon Scanning Prioritising Summary was prepared by Mr. Irving Lee from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).