



Horizon Scanning Technology Prioritising Summary

Crosseal™ fibrin sealant

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Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical



Royal Australasian
College of Surgeons



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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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:

Crosseal™ fibrin sealant (OMRIX Biopharmaceuticals, Ltd., Belgium).

Purpose and Target Group:

Crosseal™'s main purpose is to achieve rapid haemostasis during various surgical procedures. It is a second-generation fibrin sealant that is notably different in its formulation compared to first-generation sealants as it is based on a concentrate of human clottable proteins and highly purified native human thrombin. It does not contain any components that are based on bovine thrombin and purified fibrinogen, collagen or synthetic compounds.

Stage of Development (in Australia):

 Not yet emerged in Australia

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

Crosseal™ is not listed or registered in the Australian Register of Therapeutic Goods (ARTG).

International Utilisation:

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

Impact Summary:

Background

Fibrin sealants or fibrin glues are made from donor blood plasma. Its main components are concentrated fibrinogen and thrombin. In the 1980s, chemical and cryoprecipitation methods were employed to produce fibrinogen for use in fibrin sealants. The first fibrin sealant to gain approval by the FDA was Tisseel (Baxter Healthcare Inc.) in 1998. While fibrin sealants have been used in Europe for 25 years, the delay of approval in the United States was mainly due to the perceived risk of viral transmission from pooled human plasma. To date, fibrin sealants have been used in a wide variety of clinical applications in the US, including maintaining haemostasis in cardiopulmonary bypass, splenic trauma, liver resection and sealing of colonic anastomoses.



Fibrin sealants have several distinct advantages over other means of achieving homeostasis such as sutures and staples. Most notable are its relatively ease to use and excellent haemostatic results. In addition to this, fibrin sealants have been shown to be well tolerated and adverse events are scarce (Le Guehennec et al. 2004). However, there have been recent reports of increasing incidences of anaphylactic shock caused by the bovine-derived components (aprotinin) in fibrin sealants (Schwartz et al. 2004). The possibility of a hypersensitive reaction due to immunoglobulin E antibodies acting against bovine aprotinin is rare in individuals without prior exposure, but the risk increases to 5% between two weeks and six months after the first exposure (Spotnitz et al. 2005).

Crosseal™ (known as Quixil® outside the United States) is a second-generation, virally inactivated surgical sealant. It is produced from concentrated human clottable proteins, namely biological active component (BAC), which contains the active component fibrinogen, and human α -thrombin (1000IU/ml) (Schwartz et al. 2004). Crosseal™ does not contain aprotinin (tranexamic acid is used in place of aprotinin), and hence the risk of anaphylactic reactions in susceptible patients is greatly reduced (Vaiman *et al.* 2005). This fibrin sealant is applied using an application device which drips/sprays Crosseal onto the bleeding site.

Clinical Need and Burden of Disease

The ability to maintain haemostasis during surgery is essential for patient survival and recuperation. While many products that have been developed for this purpose Crosseal™ is the only agent not to contain bovine derived proteins. This may be a considerable advantage due to its potential in preventing anaphylactic reactions that may occur in certain patients.

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

Crosseal™ is widely diffused in Europe, the United States and the United Kingdom having been used in over 7000 patients undergoing a variety of surgical procedures. Considering its ease of use and minimal risk of causing allergic reactions it would be reasonable to expect widespread and fast diffusion once its safety and efficacy is established and the product is approved in Australia.

Existing Comparators (aside from standard methods of haemostasis)

- Tisseel (Baxter Healthcare Inc.)
- Avitene (CR Bard)
- Gelfoam (Pharmacia & Upjohn)



- Oxycel (Parke-Davis)
- Surgicel (Ethicon)
- Surgicel Nu-Knit (Ethicon)
- Thrombin-JMI (King Pharmaceuticals)
- All other surgical sealants used for achieving haemostasis

Estimated Cost Impact

In the United States, Crosseal™ is priced at ~US\$100 per ml (Vaiman *et al.* 2003); its exact cost in Australia is not known. In contrast to Tisseel which retails for ~ US\$66 per ml (MacGillivray 2003), Crosseal™ costs significantly more.

Efficacy and Safety Issues

List of Studies Found

Total number of studies	5
Randomised controlled trials	5 (6 papers)

The studies included in this summary are highlighted in bold in the reference list.

Safety and efficacy data from five randomised controlled trials have been selected for inclusion in this summary. These studies represent the body of evidence currently available for this product.

The efficacy of Crosseal™ as a haemostatic agent compared to standard topical hemostatic agents after liver resection was examined by Schwartz *et al.* (2004) (results of this study were reported in the FDA summary as well). Patients were randomly allocated into the Crosseal™ group (n=58) and the control group (standard haemostatic agents) (n=63). At the end of the study, 55 patients from the Crosseal™ group (three excluded; one did not received Crosseal™, two received concomitant medication that was not permitted) and 61 patients from the control group (two excluded as they did not receive control treatment) were efficacy-evaluable. Mean time to haemostasis was significantly shorter in the Crosseal™ group (282 seconds) compared to the controls (468 seconds) (p=0.006). Treatment with Crosseal resulted in an estimated 22.4% reduction in time to haemostasis (95% CI, 7.1%-35.1%). When the excluded patients were integrated into the analysis, the mean time to hemostasis remained shorter in the Crosseal™ group than the control group (318 seconds and 462 seconds respectively) (p=0.02). The percentage of patients who achieved



haemostasis within ten minutes was significantly greater in the Crosseal™ group (91.4%) compared to the control group (69.8%) ($p=0.003$).

Crosseal™ was shown to be a superior haemostatic agent compared to conventional nasal packing after endoscopic sinus surgery (ESS) (Vaiman et al. 2005). In the nasal packing group, various complications were recorded; all 32 patients in this group complained of breathing disturbance during sleep, 14 patients complained of lacrimation while 18 complained of pain and intranasal pressure due to the packing. Mucus discharge was common in this group, contrasting the Crosseal™ group where these complications were not reported. Haemorrhage was reported in seven patients (21.87%) after nasal pack removal, which is significantly higher than the Crosseal™ group ($p<0.001$). Six patients experienced slight reactive bleeding after nasal pack removal (18.75%) while one patient (3.12%) had bleeding through the nasal packing. There was one case (3.12%) of significant bleeding after pack removal thus requiring a replacement pack. Endoscopic evaluation of Crosseal™ patients revealed no postoperative swelling, synechiae, atrophic changes, or adhesions. There was however one case (3.12%) of late postoperative bleeding in the Crosseal™ group 48 hours after the operation. No allergic reactions to the fibrin glue were documented.

Vaiman *et al.* (2003) looked at the potential of Crosseal™ as a substitute for electrocautery and other haemostatic techniques in tonsillectomy. Patients were randomly allocated to the Crosseal™ group ($n=87$) and bipolar electrocautery group ($n=92$). All patients in the Crosseal™ group achieved complete haemostasis and resolution of major symptoms. Additionally, all patients had good tissue healing with no inflammation, plaques or crusts. No allergic reactions were reported. The average intraoperative blood loss in Crosseal™ patients was 15mL and there were no incidents of post-tonsillectomy haemorrhage. In contrast, patients in the bipolar electrocautery group experienced swelling, pain and slow wound healing. Average intraoperative blood loss was 29mL for needle point electrocautery and 33mL for bipolar coagulation, considerably more compared to the fibrin glue group ($p<0.005$). Post-operative bleeding occurred in 4% (4 patients) of patients in the bipolar electrocautery group, significantly higher than the fibrin glue group ($p<0.01$). One patient experienced bleeding after vigorous exercise, two patients did not have a specific cause for the bleeding, and the last patient suffered secondary haemorrhage due to local tissue necrosis.

Wang et al. (2001) investigated the haemostatic efficiency of Crosseal™ in 53 patients undergoing unilateral primary total knee arthroplasty with cement. Patients were randomised into a control group ($n=28$) and the Crosseal™ group ($n=25$). Twelve hours after the operation, drainage was a mean of 184.5[28.9]^{SE} mL for the Crosseal™ group (data collected from 23 patients) and 408.3[54.6]^{SE} mL for the control group (data collected from 23



patients). Patients of the Crosseal™ group had mean haemoglobin levels of 114.8[2.7]^{SE} g/L on the first post-operative day and patients in the control group had mean haemoglobin levels of 104.9[2.6]^{SE} g/L (data collected from 24 patients) on the first post-operative day. Drainage within 12 hours post-operatively (after time adjustment) in the Crosseal™ group was 55.6% less (95% CI 27.1 to 73.0) than the control group (p=0.002). Additionally, after adjusting for pre-operative haemoglobin levels, the decrease in haemoglobin for Crosseal™ patients on the first post-operative day was 28.9% less (95% CI 10.2 to 43.7) compared to the controls (p=0.005). Wang et al. (2001) reported the development of a hematoma in one Crosseal™ patient (4%) while four patients (14%) in the control group developed this condition.

The efficacy of Crosseal™ as a haemostatic agent was further investigated in patients undergoing total knee arthroplasty (Levy et al. 1999). Twenty nine patients were randomised to the Crosseal™ group while another 29 patients were allocated to the control group (standard haemostasis). Mean apparent post-operative blood loss was significantly lower in the Crosseal™ group (360[287.7]^{SD} mm) compared to the 878 [403.0]^{SD} mm blood loss in the controls (p<0.001). Additionally, the Crosseal™ group had a mean decrease of haemoglobin concentration of 25[10]^{SD} g/L, significantly less compared to 37[12]^{SD} g/L in the control group (p<0.001). Levy et al. (1999) also determined the calculated blood loss, the figures obtained for both groups were much higher compared to the apparent/observed blood loss (Crosseal™ group = 1063.0[481.95]^{SD} mm, control group = 1768.0 [614.60]^{SD} mm), but the Crosseal™ group retained a significantly lower calculated blood loss value (p<0.001). Furthermore, only five patients (17%) from the Crosseal group required blood-transfusion (one patient [3%] required two units of blood) while 16 patients (55%) in the control group required transfusion (8 patients (28%) required two units of blood) (p=0.004). No adverse events that occurred in this study were considered to be related to the treatment (Levy *et al.* 1999).

Ethical Issues

Please refer to 'cultural or religious considerations' below.

Cultural or Religious Considerations

Patients with certain religious beliefs may not approve of the use of human blood derivatives in the formulation of Crosseal™.

Other Issues

OMRIX Biopharmaceuticals Inc. has issued a warning that Crosseal™ must not be used in contact with cerebrospinal fluid or dura mater. This is due to the fact that Crosseal™ contains tranexamic acid as an antifibrinolytic; this acid has been reported to cause



hyperexcitability, convulsions and even death as a result of γ -aminobutyric acid receptor antagonism in animal models (Spotnitz et al., 2005). Additionally, it should not be injected directly into the circulatory system or any tissue.

In May 2005, Crosseal™ was approved in the United Kingdom for use in supportive treatment during surgery for improvement of haemostasis where conventional surgical techniques are insufficient, thus extending the indications for this fibrin sealant (Medical News Today 2005).

Conclusion:

A reasonable amount of high level evidence (5 randomised controlled trials) indicates that Crosseal™ has safety and efficacy advantages compared to conventional methods of haemostasis. However no studies comparing second generation fibrin sealants (Crosseal™) with older fibrin sealants were located. It is not clear whether Crosseal™ is safe and effective for all types of surgery. It however improves haemostasis in knee arthroplasties, tonsillectomy, endoscopic sinus surgery and liver resection. It is not known whether Crosseal™'s advantage in terms of reduced anaphylactic incidences offset its relatively high cost compared to first generation fibrin sealants.

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

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Sources of Further Information:

OMRIX Biopharmaceuticals. Last updated 2005. <http://www.omrix.com> [Accessed July 2005].

Search Criteria:

A search of MEDLINE, PubMed and Cochrane Library, Current Controlled Trials metaRegister, UK National Research Register, International Network for Agencies for Health Technology Assessments, relevant online journals and the Internet was conducted in June 2005.

Search terms used were: 'Crosseal', 'Quixil', 'OMRIX fibrin seal\$', and 'second generation fibrin seal\$'

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).