Health Policy Advisory Committee on Technology

Technology Brief

LeGoo®: reverse thermosensitive polymer gel for the temporary occlusion of blood vessels during surgery

May 2012
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This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospital Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Dr Vicki Foerster and Dr Prema Thavaneswaran for the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
TECHNOLOGY BRIEF

REGISTER ID  WP098

NAME OF TECHNOLOGY  LeGoo® reverse thermosensitive polymer gel

PURPOSE AND TARGET GROUP  FOR TEMPORARY OCCLUSION OF BLOOD VESSELS DURING SURGERY

STAGE OF DEVELOPMENT IN AUSTRALIA

☑  Yet to emerge
☐  Experimental
☐  Investigational
☐  Nearly established
☐  Established
☐  Established but changed indication or modification of technique
☐  Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐  Yes  ARTG number: Not applicable
☒  No
☐  Not applicable

INTERNATIONAL UTILISATION

<table>
<thead>
<tr>
<th>COUNTRY</th>
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<tr>
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**IMPACT SUMMARY**

LeGoo® is a reverse thermosensitive polymer gel manufactured by Pluromed Inc (Woburn, Massachusetts, USA), that temporarily occludes blood vessels with the aim of controlling bleeding during surgery. The product is not approved for use in Australia, although it received a CE mark for Europe in 2007 and Food and Drug Administration (FDA) approval in late 2011. The technology would be made available through hospitals for use by surgeons, particularly cardiac and vascular surgical specialists. The main indication identified in the literature was off-pump coronary artery bypass graft (OPCABG) surgery, with several small case series describing the use of LeGoo® in peripheral artery bypass procedures. Other indications have been suggested by the manufacturer. Comparator techniques that are used to control bleeding during OPCABG surgery include intracoronary shunts, clamps, vessel loops, snares and CO₂ blowers; however, these can cause problems such as endothelial dysfunction and vessel dissection, and also crowd the surgical field. Available studies of LeGoo® (generally sparse and low quality) report that the technology is efficacious and safe, being at least as good as or superior to conventional technologies. The learning curve for surgeons is short. LeGoo® shows potential to be a novel tool for temporary vessel occlusion in the surgical setting, although the cost-effectiveness of this technology is yet to be determined.

**BACKGROUND**

Poloxamer 407 is a non-toxic gel from a family of biocompatible, water-soluble polymers that possess reverse, thermosensitive properties, i.e., as the temperature increases, viscosity increases (FDA 2011). LeGoo® is comprised of 20 per cent poloxamer 407 and is a non-toxic, non-absorbed, and non-metabolised substance that is a viscous liquid at room temperature, converting to a solid gel instantly when exposed to body temperatures (Wimmer-Greinecker et al 2011).

LeGoo® is injected into a blood vessel that is intended to be occluded, with the injected amount determined by vessel diameter. An arteriotomy is made at a desired location, the cannula is inserted proximally, and LeGoo® is injected against blood flow (FDA 2011). Importantly, the product is only indicated for use in blood vessels below the neck up to 4 mm in diameter, and is contraindicated for use in patients with vascular anatomy or blood flow that precludes cannula placement or proper injection and control of LeGoo® (FDA 2011).

Intravascular administration produces a firm gel plug that allows work in a comparatively bloodless surgical field. When injected into a blood vessel, an occlusive plug conforms to lumen contour, even when the lumen is distorted by arterial disease. A cylindrical vessel shape is maintained and can be pierced with a
surgical needle, facilitating suturing. The gel dissolves spontaneously after 10-20 minutes, or instantly by topical application of crushed ice or iced saline. Once dissolved, LeGoo® cannot reform a gel because the concentration is too low. The diluted material passes through the microcirculation and is excreted in urine (Wimmer-Greinecker et al 2011; Kretz et al 2012; Pluromed 2012).

According to the manufacturer, LeGoo® provides ‘atraumatic occlusion [for] blood-free anastomosis’. The manufacturer suggests that the product (Pluromed 2012):
- exerts no radial pressure (unlike clamps, loops, or balloons)
- will not crush fragile or calcified vessels
- provides a superior surgical field
- minimises dissection
- stents vessels for easier suturing and can be sewn through
- enables a shorter time of occlusion and anastomosis
- can be dissolved at will to restore flow.

LeGoo® is supplied in prefilled syringes as a sterile, single-use product with a soft olive-tipped cannula. It is available in volumes ranging from 0.25 to 2.5 mL to accommodate a range of vessel sizes and desired plug lengths (Wimmer-Greinecker et al 2011; Pluromed 2012). The learning curve for use by surgeons is short, including determination of the right quantity of material required (Shalhoub et al 2011). A reference guide is included with LeGoo®’s commercial materials (Pluromed 2012).

The manufacturer indicates that LeGoo® can be used in cardiac and peripheral vascular surgery, microsurgery (plastics, reconstructive, etc) (Pluromed 2012), as well as in organ transplant and lung, kidney and liver surgery (Pluromed 2009). An additional indication is in creation of arteriovenous fistulae for patients who require haemodialysis (Kretz et al 2012). The main clinical indication for LeGoo® that is reported in the published literature is OPCABG, a surgical procedure that is performed to relieve angina and reduce the risk of death from coronary heart disease (CHD). This ‘beating heart’ surgery is a less invasive alternative to conventional coronary artery bypass graft (CABG) surgery and aims to avoid the surgical trauma caused by cardiopulmonary bypass. OPCABG can be achieved via median sternotomy or by a less invasive procedure called minimally invasive direct coronary artery bypass (MIDCAB).

**Clinical Need and Burden of Disease**

Based on self-reported data from the 2007–08 National Health Survey, approximately three per cent of the Australian population suffer from CHD (AIHW 2011). In 2003, CHD was responsible for approximately 11 per cent of the overall disease burden for males and 9 per cent of the overall disease burden for females...
(Begg et al 2007). The majority of the overall CHD burden for both males (79%) and females (85%) was due to premature death (AIHW 2011).

In Australia, an estimated 17 per cent of CABG procedures are performed off-pump (MSAC 2001). Several CABG procedures are currently listed on the Medicare Benefit Schedule (MBS), however only three of these procedures (Item numbers 38498, 38501, and 38504) are performed without cardiopulmonary bypass. Based on MBS data, a total of 334 claims were made for services covered by the item numbers listed above, between July 2010 and June 2011 (Medicare Australia 2012).

In 2007–08, there were a total of 161,417 hospitalisations in Australia with a principal diagnosis of CHD, representing 2 per cent of all hospitalisations (AIHW 2011). In 1999–2000, the average length of stay for hospitalisations with CHD (excluding same day hospitalisations) was 6.4 days, and this remained essentially unchanged until 2007–08 (AIHW 2011).

CHD was the leading cause of death in Australia in 2007, accounting for 17 per cent of all deaths, with more than half of these deaths occurring as a result of acute myocardial infarction (AIHW 2011). In 2007-08, 3.6 per cent of CHD hospitalisations ended in death (AIHW 2011).

DIFFUSION OF TECHNOLOGY

Australia
Le Goo is not registered on the Australian Register of Therapeutic Goods, and there is no evidence that LeGoo® has been employed in Australia, either in a research capacity or via uptake in surgical suites. However, French pharmaceutical giant Sanofi has recently stated an intent to purchase LeGoo®’s manufacturer, Pluromed Inc, and an enhanced marketing plan is expected (Fox Business News 2012; Sanofi Biosurgery 2012).

Other countries
Studies assessing LeGoo® have been completed in the USA, Canada, the United Kingdom, France, Germany, Italy and the Netherlands. The product received a CE mark in 2007 and was approved by the FDA in September 2011. LeGoo® is also being marketed in more than 25 countries in Europe and Asia (FDA 2011).

COMPARATORS
In complex surgery such as coronary procedures, a bloodless field is crucial for clear visualisation and accurate placement of sutures; however, many temporary occlusive devices for coronary surgery including intracoronary shunts, clamps, vessel loops, snares and CO₂ blowers, risk damage to blood vessels (Bouchot et al 2010; Rastan et al 2010; Wimmer-Greinecker et al 2011). Study authors assert that these traditional devices and techniques can cause endothelial dysfunction, coronary wall injury or
coronary vascular dissection – or air embolism in the case of CO₂ blowers. They are not always effective in controlling collateral and retrograde coronary blood flow and crowd the operative field, potentially making procedures more difficult (Bouchot et al 2010; Rastan et al 2010; Shalhoub et al 2011; Wimmer-Greinecker et al 2011).

SAFETY AND EFFECTIVENESS ISSUES

Three studies assessing LeGoo® were included in this brief, all for patients undergoing OPCABG: a manufacturer-sponsored randomised controlled trial (RCT) (Wimmer-Greinecker et al 2011), a time series study (Rastan et al 2010) and a case series study (Bouchot et al 2010).

Wimmer-Greinecker et al (2011)

The purpose of this RCT (level II intervention evidence) was to compare the feasibility, safety, and efficacy of LeGoo® to vessel loops in obtaining a bloodless anastomotic field during OPCABG (Table 1). Participating surgeons were required to have experience using LeGoo® in at least five previous cases. At baseline, patient characteristics for the two study arms were not significantly different. Patients were followed-up for 30 days after surgery.

This study tracked major adverse cardiac events (MACE) as a study endpoint, including death from all causes, graft occlusion, low cardiac output syndrome, and myocardial infarction intraoperatively or up to 30 days following surgery. MACE rates were similar between groups at 6.3 per cent (3/48) for LeGoo® and 6.5 per cent (3/46) for controls. One death (1.8%) occurred in a patient with LeGoo® but further investigation attributed this to a rare hereditary coagulopathy. No deaths were reported in the control arm. Three patients (5.5%) in the LeGoo® arm had graft occlusions versus none in the control arm. One patient each in the LeGoo® (2.1%) and control (2.2%) arms suffered myocardial infarction. The rate of surgical, cardiac, pulmonary and other complications were not significantly different between the groups.

The primary study endpoint was degree of haemostasis in the surgical field using a 4-point semi-quantitative scale ranging from 1 (excellent haemostasis) to 4 (poor haemostasis/copious bleeding). Satisfactory or excellent haemostasis was achieved in 88 per cent of LeGoo® cases versus 61 per cent of controls (p<0.0001). Other key efficacy outcomes are described in Table 2.
Rastan et al (2010)
This time series study (level III-2 intervention evidence) aimed to evaluate the safety and efficacy of LeGoo® during MIDCAB at a single institution, with a single surgeon (Table 1). At baseline, patients in the two study arms were not significantly different aside from a higher rate of previous percutaneous coronary interventions in the control group. The mean length of follow-up was 317 ± 21 days.

The authors stated that there were no negative postoperative events associated with the use of LeGoo®, nor any major cerebral or cardiovascular events, or mortality in either group.

The subjective sense of site visibility was superior for the LeGoo® group compared with the control group (no measurement scale or other details were provided). Other key efficacy outcomes are described in Table 2.

Bouchot et al (2010)
This case series study (level IV intervention evidence) examined the outcomes for patients undergoing OPCABG under a single surgeon at one hospital (Table 1). The study protocol specified that LeGoo® would be used for all coronary anastomoses but if the operative field was obscured by blood or there was evidence of myocardial ischaemia, traditional technologies would be employed.

The following complications were reported, each in one patient:

- Excessive bleeding from the epicardium
- ST-segment elevation and life-threatening tachyarrhythmia 4 minutes after deployment of LeGoo® (LeGoo® was dissolved and replaced with an internal shunt, normal sinus rhythm returned, the ST-segment elevation receded, and the operation was completed without further problems)
- ST-segment elevation on post-operative day 1 with angiogram evidence of left internal mammary artery stenosis treated with coronary artery bypass (using LeGoo®)
- Myocardial infarction
- Transient ischemic attack (recent history of cerebrovascular accident)

In addition, six patients developed atrial fibrillation that responded to amiodarone with return of normal sinus rhythm.

The surgeon rated the degree of haemostasis according to a 4-point scale from excellent (no bleeding into anastomotic field) through good and fair to poor (profuse bleeding, continuous use of blood removal device); excellent and good were considered ‘satisfactory’ to provide a sufficiently bloodless field. Results showed that in 90 per cent of vessels, satisfactory results were achieved with LeGoo®, with 60 per cent requiring only one LeGoo® injection. Other key efficacy outcomes are described in Table 2.
<table>
<thead>
<tr>
<th>Authors; Location; Study dates</th>
<th>Study Type &amp; Level of Evidence</th>
<th>Patient Enrollment</th>
<th>Inclusion Criteria (Exclusion criteria)</th>
<th>Selected Patient Characteristics</th>
<th>Outcomes Assessed</th>
</tr>
</thead>
</table>
| Wimmer-Greinecker et al (2011); Germany, Canada, France & the Netherlands (9 centres); study dates 20 months in 2008-2010 | RCT (Level II evidence) | n=110 adults undergoing OPCABG; 56 randomised to LeGoo® (117 anastomoses) & 54 to conventional vessel loops (122 anastomoses) | • Ages 18-79  
• Elective OPCABG with at least one proximal coronary stenosis > 70%  
Selected exclusion criteria: LVEF < 40%, LMCS > 50%, previous cardiac surgery, EuroSCORE > 10, urgent or emergent surgery | • Mean age, 64 years  
• % male, 83%  
• LVEF, 61%  
• DM, 23%  
• PVD, 19%  
• Extent of disease:  
  1 vessel, 23%  
  2 vessel, 29%  
  3 vessel, 47%  
  4 vessel, 1% | • Degree of satisfactory haemostasis  
• Mean total anastomotic time  
• Cross-overs between study arms  
• Need for additional methods of haemostasis for LeGoo® patients  
• Conversion rate from OPCABG to CABG |
| Rastan et al (2010); Germany; 2 months in 2009 | Time series (Level III-2 evidence) | n=20 consecutive adults; first 10 received proximal vessel loops + CO₂ blower (controls); next 10 received LeGoo® | • Patients undergoing MIDCAB via a single surgeon with bypass of the LADA by LIMA | • Mean age, 64 years  
• % male, 80%  
• LVEF, 61%  
• DM, 10%  
• PVD, 5%  
• Previous cardiac surgery, 10%  
• LADA occlusion, 25%  
• Extent of disease:  
  1 vessel, 60%  
  2 vessel, 30%  
  3 vessel, 10% | • Procedure time  
• Subjective sense of site visibility  
• Need for CO₂ blower for LeGoo® patients  
• LIMA-LADA bypass flow measurements  
• CK-MB levels @ 4 hours, 1 day & 2 days post-op  
• Conversion rate to CABG  
• Readmission / survival |
| Bouchot et al (2010); France & USA; 27 months in 2007-2009 | Case series (Level IV evidence) | n=50 consecutive adults (99 coronary arteries) | • Patients with symptomatic CAD undergoing OPCABG via a single surgeon | • Mean age, 65 years  
• % male, 84%  
• Surgery was elective, 86%  
• LVEF > 50%, 74%  
• DM, 28%  
• PVD, 14%  
• Recent MI, 20%  
• Extent of disease:  
  1 vessel, 26%  
  2 vessel, 58%  
  3+ vessel, 28% | • Degree of satisfactory haemostasis (quality of bloodless field)  
• Need for additional methods of haemostasis  
• Number of LeGoo® injections required per vessel  
• Conversion rate to CABG  
• Complications / AEs |

AE = adverse events; CABG = coronary artery bypass graft; CAD = coronary artery disease; DM, diabetes mellitus; LADA = left anterior descending artery; LIMA = left internal mammary artery; LMCS = left main coronary stenosis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MIDCAB = minimally invasive direct coronary artery bypass; OPCABG = off pump coronary artery bypass graft; PVD = peripheral vascular disease
## Table 2  Efficacy results from included studies

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Efficacy Outcomes</th>
</tr>
</thead>
</table>
| Wimmer-Greinecker et al (2011) (RCT; n=110 – 56 in LeGoo® arm, 54 in control arm) | - *Degree of satisfactory haemostasis according to a semi-quantitative 4-point scale:* 88% of anastomoses for LeGoo® (103/117) versus 61% of anastomoses for conventional VLs (controls) (74/122); *p*<0.0001  
- *Mean total anastomotic time:* 12.8 minutes LeGoo® vs 15.4 minutes VLs; *p*<0.001 (more time required for vessels on the posterior and lateral heart walls versus the anterior wall)  
- *Cross-overs between study arms:* 2 anastomoses crossed over from LeGoo® to the control arm; 3 anastomoses crossed over from the control arm to LeGoo®  
- *Need for additional methods of haemostasis for LeGoo® patients:* 5/117 (5%) anastamoses  
- *Conversion rate from OPCABG to CABG:* 0 |
| Rastan et al (2010) (time series; n=20 of which the first 10 had regular haemostasis technology & the next 10 had LeGoo®) | - *Procedure time:* NSD between groups  
- *Subjective sense of site visibility:* Better for LeGoo® (no scale or details provided)  
- *Need for CO2 blower (traditional technology) for LeGoo® patients:* 30% (3 of 10)  
- *LIMA-LADA bypass flow measurements:* NSD between groups  
- *CK-MB levels:*  
  - 4 hours post-op: Lower for LeGoo® (13.2 vs 18.2; *p*=0.006)  
  - 1 & 2 days post-op: NSD between groups  
- *Conversion to CABG rate:* 0  
- *Readmission / survival at follow-up:* 1 patient readmitted per group for reasons unrelated to initial procedure; 100% survival in both groups |
| Bouchot et al (2010) (case series; n=50 patients & 99 grafts) | - *Degree of satisfactory haemostasis (quality of bloodless field):* Excellent 59%, good 31%, fair 9% (both excellent & good [total 90%] provided adequate visibility for accurate suturing)  
- *Need for additional methods of haemostasis:* 6/99 vessels (6%)  
- *Number of LeGoo® injections required per vessel:* 60% required one injection, 32% required two, 8% required three  
- *Conversion to CABG rate:* 0 |

AE = adverse events; CABG = coronary artery bypass graft; CK-MB = creatine kinase-MB fraction; LADA = left anterior descending artery; LIMA = left internal mammary artery; MI = myocardial infarction; NSD = not significantly different; OPCABG = off pump coronary artery bypass graft; VL = vessel loops

### Cost Impact

The manufacturer, Pluromed Inc, was contacted for costing details relating to LeGoo®; however, no information was forthcoming prior to the finalisation of this brief. The Australian and international offices of Sanofi, the company which is in the process of acquiring Pluromed Inc, were also contacted for costing details relating to LeGoo®; however, these enquiries were unsuccessful.

No cost-effectiveness information on this technology was identified. The only cost data identified was a quote of €240 per 0.5 mL LeGoo® syringe (Agostini et al 2010).

### Ethical, Cultural or Religious Considerations

No issues were identified from the retrieved material.

### Other Issues

No upcoming clinical trials assessing LeGoo® were identified.

The RCT by Wimmer-Greinecker et al (2011) was supported by the manufacturer, and LeGoo® was supplied by the manufacturer at no cost for the other two included
studies (Rastan et al 2010; Bouchot et al 2010). One author of the case series (Bouchot et al 2010) disclosed a financial relationship with Pluromed. No conflict of interest information was provided by Rastan et al (2010), and therefore the conflict of interest status of this study is unknown.

The studies included in this brief suffered from a number of limitations, including the lack of blinding, the lack of confirmation of vessel patency, the subjective nature of assessment of site visibility and the lack of long-term follow-up.

**SUMMARY OF FINDINGS**

Although the evidence is sparse and of generally low quality (only one small, manufacturer-sponsored RCT is available), LeGoo® may offer a novel alternative to conventional technologies used for temporary vessel occlusion in complex surgeries. The product has been available in Europe since 2007 and is being marketed in more than 25 countries in Europe and Asia. FDA approval was granted in late 2011, although LeGoo® is not yet approved for use in Australia. Study results showed that LeGoo®’s efficacy is equal to traditional occlusion techniques with studies showing high levels of satisfactory operative field visualisation. Significant safety issues have not been identified. No additional studies appear to be underway, although the manufacturer (Pluromed Inc) is poised for sale to a larger competitor (Sanofi), and this may impact research and marketing efforts.

**HealthPACT Assessment:**

LeGoo® is an effective method of vascular occlusion during OPCABG surgery. Although significant safety issues were not reported, a recent study by Winkler et al (2011) indicated that the gel may cause significant endothelial damage, and result in changes in response to vasoactive substances. In addition, LeGoo® is associated with a higher cost of treatment. There is at present an enthusiastic effort to distribute LeGoo® in New Zealand hospitals, and as Sanofi has recently purchased the previous manufacturer (Pluromed), it is anticipated that the marketing effort and subsequent number of centres using LeGoo® will expand. As a result, HealthPACT wishes to monitor the technology, with the objective of conducting a reassessment in 24 months.

**Number of Studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT web site.

| Total number of included studies | 3 |
| Total number of level II intervention evidence studies | 1 |
Total number of level III-2 intervention evidence studies 1
Total number of level IV intervention evidence studies 1

REFERENCES


**SEARCH CRITERIA TO BE USED**

LeGoo  
Reverse thermosensitive polymer  
Poloxamer/therapeutic use/toxicity/adverse effects  
Hemostasis, Surgical/methods  
Blood Loss, Surgical/prevention & control  
Bloodless Medical and Surgical Procedures/adverse effects