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Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Technology Prioritising Summary

Apligraf® for burns injuries

December 2005
(Updated February 2007)



ASERNIP/S

**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:

Apligraf® [Graftskin™] (produced by Organogenesis Inc. and distributed by Novartis Pharmaceutical Corp.).

Purpose and Target Group:

Apligraf® is a living, bi-layered skin substitute, indicated for use in venous and neuropathic diabetic foot ulcers that have not responded to conventional therapy. Several studies have also addressed the potential role of Apligraf® in treating burn injuries and a variety of chronic and acute wounds.

Stage of Development (in Australia):

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

Apligraf® is not yet registered with the TGA and does not have an ARTG number.

International Utilisation:

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

Impact Summary:***Background***

The management of burns involves replacing the lost tissue with a material to restore the epidermal barrier function to protect and stimulate the wound bed. This creates an improved environment for epidermal regeneration by providing a barrier against infection and controlling water loss. The gold standard for surgical repair is the use of a skin graft or flap harvested from the patient's own undamaged skin (an autograft) (Jones

et al. 2002). Alternatively, a donor graft from cadaver skin (an allograft) or a graft or flap derived from animal skin products (a xenograft) may be used.

The manner in which wounds are managed depends on their nature. Chronic wounds, such as venous stasis ulcers and neuropathic ulcers are currently treated with compression therapy, while excisional wounds that are too large to heal by secondary intention can be treated with direct closure, skin grafting or skin flaps (Taylor & Bayat 2003).

However, if none of these methods are effective, or wound complications develop, then bioengineered skin substitutes offer an alternative for wound management.

Apligraf® is a bioengineered skin substitute, composed of living fibroblasts and keratinocytes, derived from neonatal foreskin and propagated in culture. Initially, dermal fibroblasts are combined with type I bovine collagen. These cells form a dermal matrix to which keratinocytes are added to form an epidermal layer. The epidermal layer is then exposed to air, allowing the keratinocyte component to mature by re-epithelialisation. The fibroblasts in this construct are viable, reproducing cells. Apligraf® resembles human skin histologically, makes matrix proteins and growth factors and if wounded, can heal itself (Bello *et al.* 2001).

Significantly, Apligraf® is immunologically inert. Apligraf® lacks the immunogenic Langerhans' cells (due to the serial culture of the keratinocytes), melanocytes, macrophages, lymphocytes and other structures such as blood vessels, hair follicles and sweat glands. This ensures that the grafts are well-tolerated and not rejected by the graft recipient (Eaglstein & Falanga 1998).

The exact mechanisms by which Apligraf® promotes wound healing are yet to be established. It has been hypothesised that Apligraf® may perform one or more functions in wound healing. It may serve as a biological dressing that promotes healing by secondary intention, or allow the wound to heal by graft take, with remodelling of the tissue over time as host cells replace donor keratinocytes. Grafts may also deliver growth factors to wounds to expedite healing (Falanga 2000).

Apligraf® was approved for use by the United States Food and Drug Administration (FDA) in 1998 for the treatment of non-infected partial and full thickness skin ulcers due to venous insufficiency, which have not adequately responded to conventional ulcer therapy (in conjunction with standard therapeutic compression). It has also been approved for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration that have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure (FDA Summary of Safety and Effectiveness Data 2000).

Clinical Need and Burden of Disease

In Australia, fires, burns and scalds account for a relatively small proportion of injury related deaths. Burn injury can have serious long term physical and social effects, as well as economic consequences. In 2002, 1.5% of all injury related deaths were caused by burns, with males having higher death rates (72 males per 100,000) than females (43 females per 100,000) (Australian Institute of Health and Welfare 2004). Young children and the elderly are particularly vulnerable to serious injury and death from fire, burns and scalds.

The impact of burn injuries on the health economy is great. Approximately 6,248 people were hospitalised for burns in public hospitals in Australia between 2001 and 2002 (Australian Institute of Health and Welfare 2004). During this time, the mean length of hospital stay of patients with burns and frostbite was 7.3 days, with an estimated cost of AU\$36 to AU\$132 million.

It has been estimated that leg ulceration affects one to two percent of the population at some point in their lives (Phua 2001, Harding *et al.* 2000). Between 80-90% of these ulcers are caused by venous insufficiency resulting from chronic diseases such as diabetes and high blood pressure (Fiveson & Scherschun 2003) and over 25% of venous ulcers recur within one year. The monetary costs of treatment for these wounds has been estimated to be US\$2400 per patient each month (Olin *et al.* 1999), with many patients requiring treatment for prolonged periods of time. This burden of disease is expected to increase with the ageing population.

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

Over 100 000 applications of Apligraf® had occurred in the United States at September 2005 after the product was granted FDA approval in 1998. Clinical trials are underway in the United Kingdom, with Novartis holding global marketing rights. If approved for use in Australia, the clinical application of Apligraf® is expected to readily diffuse in the healthcare system.

Existing Comparators (excluding standard allografts and wound care)

- TransCyte™ (Advanced Tissue Sciences Inc.) – extracellular matrix of allogenic human dermal fibroblasts. (Available in Australia)
- Integra® (Integra Life Science Corp.) – non-living extracellular matrix of collagen and chondroitin-6-sulfate. (Available in Australia)
- BioBrane® (Dow Hickman/Bertek Pharmaceuticals) – silicone, nylon mesh and collagen composite. (Available in Australia)
- Dermagraft® (Advanced Tissue Sciences Inc.) – living allogenic dermal fibroblasts. (Not available in Australia)
- Orcel® (Ortec International, Inc.) – collagen seeded with allogenic fibroblasts and keratinocytes. (Not available in Australia)
- Alloderm® (LifeCell Corporation) – acellular, de-epithelialised cadaver dermis. (Not available in Australia)

Estimated Cost Impact

The direct costs that would be associated with the clinical use of Apligraf® in Australia could not be determined. However, Jones *et al* (2002) quote the British price of Apligraf® to be £14.20 per centimetre² (approx. \$AU 33.24) (N.B. Apligraf® is manufactured in 7.5cm diameter discs available for £626.00 (approx \$AU 1465.42)). A 2003 Markov-based simulation model utilised by Redekop *et al.* estimated the costs of good wound care for diabetic ulcers in the first year of treatment at €5310 (approx. \$AU 8476.82), while the first year of good wound care in addition to Apligraf® was found to cost €4656 (approx. \$AU 7432.78) (1999 values). They concluded that treatment with Apligraf® plus good wound care resulted in a 12% reduction in costs over the first year of treatment compared to good wound care alone, with the increased ulcer-free time that

Apligraf® provided coupled with the reduced risk of amputation working to offset the initial costs of the product.

The reimbursement fees, as stated by the Medicare Benefits Schedule, for free grafting of split skin range from AU\$574.25 to AU\$1,465.95 for patients who have burns to at least 9% and no more than 50% of their total body surface area (Medicare Australia 2005a). This fee only involves excision of burnt tissue. In the July 2004 to July 2005 financial year, there were 18 claims to Medicare in this group of patients for the following item numbers: 45460, 45461, 45464, 45471, 45415 and 45418 (Medicare Australia 2005b).

The direct costs of treating wounds and burns (compression treatment, skin grafting, hospital stays etc.) do not take into account the substantial indirect costs of these conditions, such as work absenteeism, exacerbation of co-morbidities and potential recurrence of the wound requiring further medical attention.

Efficacy and Safety Issues

List of Studies Found

Total number of studies	16
Randomised controlled trials (1 donor site, 3 venous ulcers, 2 diabetic foot ulcers and 1 burns)	7 studies, 9 papers
Non-randomised comparative studies	2
Case series studies	6
Cost evaluation	1

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

Safety and efficacy data from 7 randomised controlled trials, 2 non-randomised comparative studies and 6 case series studies have been selected for inclusion in this summary, as they represent a broad range of applications for Apligraf®.

Please note that the randomised controlled trials of Apligraf® for burns and wounds will be more fully covered in the ASERNIP-S systematic review in progress as at September 2005.

Randomised controlled trials – donor sites

A randomised controlled trial (RCT) by Muhart *et al.* (1999) compared the healing of 60 skin donor sites treated with three different protocols – meshed autograft, meshed Apligraf® and polyurethane film (PUF) occlusive dressing. The average time of healing was 7.3 days (SD 0.8 days) for the Apligraf® sites, 7.6 days (SD 1.1 days) for the autograft and 9.5 days (SD, 1.8 days) for the PUF, with the healing time with Apligraf® or autograft being statistically significantly shorter than the PUF ($P < 0.001$).

Randomised controlled trials – venous ulcers

A RCT involving 240 patients by Falanga (2000) found that treating venous ulcers of greater than one year's duration with Apligraf® resulted in 47% of patients achieving wound closure at 24 weeks, compared to 19% treated with standard compression therapy ($P = 0.002$). Sabolinski *et al.* (1996) found that Apligraf® achieved a faster rate of complete wound closure in 233 patients than did the standard care of compression therapy (57 days versus 181 days, $P = 0.0066$) as well as a higher rate of complete wound closure, with 64% of Apligraf® treated patients achieving closure compared to 44% of patients treated with standard care ($P = 0.012$). A study of 293 patients (Falanga *et al.* 1998) also concluded that treatment with Apligraf® was more effective than compression therapy alone, with 63% of patients treated with Apligraf® having healed wounds after 6 months compared with 49% of patients treated with only compression therapy ($P = 0.02$) and the wounds treated with Apligraf® having a faster healing time.

Randomised controlled trials – diabetic foot ulcers

In a RCT with 208 patients (Veges *et al.* 2001), 56% of Apligraf® treated patients achieved complete wound healing compared to 38% treated with saline-moistened gauze

($P=0.0042$). The median time to complete closure was also significantly lower in the Apligraf® group (65 days compared to 90 days). A separate trial (Sabolinski and Veves 2000) involving 33 patients found that 75% of ulcers treated with Apligraf® healed completely, compared to 41% treated with the standard therapy of saline-moistened gauze ($P<0.05$). They also found the median time to complete healing was statistically significantly shorter ($P=0.01$) in the Apligraf® group (38.5 days) than in the control group (91 days).

Randomised controlled trials – burns

Waymack *et al.* (2000) used Apligraf® over meshed split thickness autografts and found that there was no difference in the percent take of the autograft in the presence or absence of the Apligraf®, or in the median number of days to greater than 75% take of the autograft. Within the 40 patient population, cosmetic and functional advantages were associated with the use of Apligraf® when compared to control sites by the clinical investigators.

Non-randomised comparative studies

Apligraf® has also been used to treat wounds after surgery. In Gohari *et al.* (2002) the incidence of complete wound healing in both the Apligraf® treated group and the secondary intention healing group was 100%, with healing at a similar rate. The wounds treated with Apligraf® were more pliable and less vascular, as defined by the Vancouver Burn Scar Assessment Scale. Allie *et al.* (2004) compared Apligraf® with standard wound care in 60 patients with leg and sternal wounds as a result of CABG surgery. They found that time to wound healing for leg wounds treated with Apligraf® ranged from 26-72 days (mean, 46 days) compared to the standard wound care group, in which healing time ranged from 34-120 days (mean, 84 days). For sternal wounds, time to healing for the Apligraf® group ranged from 21-80 days (mean, 39) and 36-110 days (mean, 62) for the standard wound care group.

Case series

In a retrospective case series examining the treatment of low extremity ulcers recalcitrant to conventional therapy in 22 patients, Delfanian *et al.* (2004) found that 64% of their study population had ulcers that healed completely in a mean time of 5 months after the application of Apligraf®. Fivenson and Scherschun (2003) also reported positive outcomes with the application of Apligraf® to 21 non-healing venous ulcers – all ulcers decreased in size, with a mean change of -2.37cm^2 per week. They also found that the use of Apligraf® resulted in lower medical costs for the five patients on whom economic data was available. In the case series of Brem *et al.* (2001), 33 patients with 54 venous ulcers of long duration achieved a frequency of complete wound closure of greater than 70% within 6 months with the use of Apligraf®.

In a separate case series, Brem *et al.* (2000) used Apligraf® to treat 41 wounds (20 diabetic foot ulcers and 21 pressure ulcers) in 23 patients. Seven out of 10 patients with diabetic wounds had all wounds heal and 86% of 20 wounds in total healed. Seven of 13 patients with pressure ulcers had all wounds heal and 13 of 21 wounds healed in an average of 29 days. Of the patients with pressure wounds that did not heal, 5 had the concurrent presence of a stage IV ulcer and 1 had a stage III ulcer, which did not heal completely before the patient's death due to unrelated causes. In the case of the diabetic ulcers, 2 of the patients had ulcers on toes in which there was necrosis of the distal phalanx, which required later amputation, while the other patient had a wound on a failed necrotic muscle flap that resisted complete healing.

Falabella *et al.* (2000) also utilised Apligraf® to treat 69 epidermolysis bullosa wounds. 82% of wounds were healed 6 weeks after being treated and patients reported a better quality of life despite some of the treated wounds not remaining healed at 18 week review.

Eaglstein *et al.* (1999) investigated the healing of acute excisional wounds treated with Apligraf® in 107 patients. It was found that after 'good to excellent persistence' of the graft in 73% of patients in the initial week, this number decreased to 31% over the follow-up period of 12 months. It was also determined that persistence of the graft was better in cases of partial thickness wounds as opposed to full-thickness wounds.

None of the randomised control trials, non-randomised comparative studies or case series reported any significant adverse effects related to the use of Apligraf®.

2007 update

Safety and efficacy

A search of relevant databases, online journals and the Internet was conducted in January 2007, following the recommendation in December 2005 that Apligraf be monitored for assessment in 12 months time. One new case series study was identified and retrieved.

The case series study (n = 10) by Hu et al. (2006) examined the persistence of Apligraf fibroblasts and keratinocytes in acute partial-thickness donor site wounds in an attempt to better understand the mechanism by which Apligraf speeds healing. In addition to this, Apligraf was compared to Apligraf without epidermis (AWE) and polyurethane film (PUF) dressing. Over the course of this study, two patients were lost to follow-up after week 8. The persistence of Apligraf and AWE cellular DNA at the donor sites were obtained via the assessment of biopsy specimens (obtained at week 1, 4 and 12) for the expression of specific human leukocyte antigen (HLA) genes by Apligraf and AWE. At 1 week post-treatment, 2/7 Apligraf treatment sites and 2/8 AWE treatment sites contained Apligraf DNA by RT-PCR. At week 4 post-treatment, 1/2 Apligraf sites and 1/2 AWE sites had positive Apligraf DNA by RT-PCR. After week 4, no persistence of Apligraf DNA was detected. These results indicate that the fibroblasts within the Apligraf dermis may be the source of the persistent DNA.

At week 1, seven of the biopsies were adequate for basement membrane component evaluation. However, immunohistochemical testing for basement membrane components (type IV collagen, laminin 5, heparin sulfate) revealed no significant difference between the three treatments. Results obtained from basement membrane analysis were consistent with the histopathology of a normal healing wound in all three treatment sites. The investigators reported that all donor sites were healed by week 8, the median healing time between the Apligraf (23 days, range: 15-55 days), AWE (21.5 days, range: 15-35 days)

and PUF (19.5 days, range: 14-34 days) sites were not significantly different. In addition, no significant difference was observed in the time to heal between wounds with persistent Apligraf DNA and those without Apligraf DNA. When wounds that had positive Apligraf DNA at either weeks 1 or 4 was compared with the two other treatment sites (AWE and PFU), no significant difference in time to healing was noted. However, it should be noted that due to the fact that donor sites were wounded from biopsies, the healing times within this study should be interpreted with caution. This may explain the discrepancy of this study to previous studies, where Apligraf was able to induce faster healing compared to PUF dressing and achieves wound healing at rate similar to autologous grafts.

Analyses found no significant differences between the treated donor sites in terms of clinician's assessments of wound healing and the cosmetic appearance of the healed wound. Vancouver Burn Scar Assessment Scale scores indicated minimal scarring across all treatment modalities, and no significant differences were observed in erythema, oedema, exudates, or wound infection among treated donor sites throughout the study. There were no incidences of clinical rejection and adverse events were comparable between the treatments. The authors reported that none of the adverse events (8 patients, 3 serious adverse events in 2 patients) were related to the use of Apligraf, AWE or PUF (Hu et al. 2006).

Overall, the investigators concluded that Apligraf's ability in speeding healing of acute wounds appears to be related to factors other than the persistence of donor (Apligraf) DNA or effect of basement membrane restoration.

2007 Recommendation

At the time of writing, the exact mechanism in which Apligraf is able to speed up healing of wound remains unknown, however it does not appear to be influenced by the persistence of Apligraf DNA. Based on the limited evidence and lack of development in the past 12 months, HealthPACT has recommended that further assessment of this technology is no longer warranted.

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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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Ethical Issues

No issues were identified from the retrieved material. However, it is of note that there is the potential for viral transmission, as Apligraf® is derived from human components. This is addressed by the manufacturers through rigorous pre- and post- partum testing of the mother and cell bank tissue for a variety of viruses (such as HIV, hepatitis, Epstein-Barr and other contaminants). The final Apligraf® construct also has to pass a stringent set of quality control measures before clinical application.

Cultural or Religious Considerations

The use of bovine collagen is unacceptable to some Hindus and Buddhists, while the use of products derived from neonatal prepuce is unacceptable to Quakers. A number of other religious groups state that informed consent in relation to the use of biological material would be required before the use of Apligraf® (Enoch *et al.* 2005). There may be other cultural and/or religious objections to these products which have not been specifically stated, while the use of bovine collagen may be unacceptable to vegans and vegetarians.

Other Issues

Dr M. Sabolinski is the Senior Vice President, Medical and Regulatory Affairs, Organogenesis.

A number of the studies have been funded partially or wholly by grants from Novartis Pharmaceutical Corp and/or Organogenesis.

Recommendation:

A significant body of evidence exists on the safety and efficacy of Apligraf® in the treatment of ulcers and other wounds. In these circumstances, Apligraf® appears to be a safe and useful adjunct to traditional therapy, particularly in the treatment of recalcitrant and complex wounds. However, there is not yet adequate information on the use of Apligraf® in the treatment of burns to determine its efficacy in these situations.

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| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

Note: ‘Bioengineered skin substitutes for the management of burns: a systematic review’ and ‘Bioengineered skin substitutes for the management of wounds: a systematic review’ are currently in progress as ASERNIP-S reviews.

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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 September 2005.

Search terms used were:

‘Apligraf’, ‘Graftskin’ and ‘Apligraf and (wounds OR burns)’

This Horizon Scanning Prioritising Summary was prepared by Ms Amber Watt 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).