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National Horizon Scanning Unit

Horizon scanning prioritising summary

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**Apligraf[®]: For the treatment of diabetic
foot and venous leg ulcers.**

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PRIORITISING SUMMARY

REGISTER ID: 000129

NAME OF TECHNOLOGY: APLIGRAF®

PURPOSE AND TARGET GROUP: TREATMENT OF DIABETIC FOOT AND VENOUS LEG ULCERS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|--|---|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | <input type="checkbox"/> Not applicable |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		
United Kingdom	✓		
Canada	✓		

IMPACT SUMMARY:

Organogenesis Inc. provides Apligraf® with the aim of treating diabetic foot and venous leg ulcers. The American Food and Drug Administration first approved Apligraf® for the treatment of hard-to-heal venous leg ulcers in 1998 and extended approval for the treatment of diabetic foot ulcers in 2000. The manufacturer plans to seek approval in the United States for three new indications, although these are not disclosed on the company website (Organogenesis Inc. 2004). Apligraf® is not yet available in Australia.

BACKGROUND

Apligraf® is a bioengineered skin product which contains Type 1 bovine collagen and is composed of neonatal fibroblasts and keratinocytes. Apligraf® is indicated for use in conjunction with standard compression therapy for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency. It is indicated for ulcers of greater than one month duration that have not responded to conventional ulcer therapy. Apligraf® is also indicated for use with diabetic foot ulcers. Apligraf® is contraindicated for use in clinically infected wounds.

Apligraf[®] is supplied as a circular disk 75mm in diameter, with a thickness of 0.75mm.

CLINICAL NEED AND BURDEN OF DISEASE

The Australian National Diabetes Information Audit and Benchmarking (ANDIAB) data for 2000 reported a 3.0% prevalence of current foot ulcers among adult patients attending diabetes clinics (AIHW 2002). The majority (86.5%) of patients with a current foot ulcer had a past history of foot ulceration. Peripheral vascular disease was recorded in a total of 12.6% of persons with diabetes, which may be indicative of potential foot ulcer problems (NADC 2000). It is estimated that approximately one million people suffer from one of the three types of diabetes (Type-1, Type-2 and gestational diabetes) in Australia. There is currently a lack of reliable incidence and prevalence data for diabetes in Australia (AIHW 2002). It is estimated that approximately one percent of the Australian population suffers from chronic leg ulceration. The most common cause is poor blood circulation. Other causes or exacerbating factors include relentless pressure (bed sores), poorly managed diabetes, high cholesterol, smoking, dietary problems and poor arterial circulation. Older people are at greater risk (Department Human Services, Victoria, 2004).

DIFFUSION

Apligraf[®] is currently not in use in Australia. In the United States Apligraf[®] has been used in a variety of clinical settings including hospitals, operating rooms, private consultants' rooms, outpatient and wound care centres (personal communication, Clinical Affairs Coordinator, Organogenesis). The substantial cost of the device and the need for repeated applications may discourage its use in clinical settings. There is also a need for further studies in the long-term to evaluate safety and effectiveness.

COMPARATORS

Treatment options for leg ulcers include compression bandages, medication, surgery and (more recently) hyperbaric oxygen therapy. Surgical alternatives for neuropathic diabetic foot ulcers include arterial bypass grafting to re-establish blood supply and skin grafting.

EFFECTIVENESS AND SAFETY ISSUES

A randomised controlled, multi-centre unblinded study (level II evidence) was conducted to evaluate the safety and effectiveness of Apligraf[®] in comparison to control treatment, saline moistened gauze, for the treatment of diabetic neuropathic foot ulcers (FDA, 2004a). The study population included patients aged between 18 and 80 years old, with a 0.4 cm² -16.3 cm² full-thickness foot ulcer of neuropathic etiology of at least 2 to 3 weeks duration, located on the plantar, medial or lateral surface of the foot, at least 2 cm away from any other ulcers on the same extremity.

There were 208 patients treated in this study; 112 received Apligraf[®] and 96 received control therapy (saline gauze). Patients received 12 weeks of treatment and 3 additional months of follow-up. Complete wound closure was evaluated by, or at 12 weeks. Patients were evaluated weekly for the first 12 weeks with mid-week visits for dressing changes from Day 0 through Week 5 and follow-up visits at Months 4, 5 and 6. In addition there was a statistically significant improvement in the incidence of ulcer closure per unit time when compared to control therapy of 56% (63/112) for Apligraf[®] and 38% (36/96) for control patients by, or at, 12 weeks (p=0.0082) (FDA, 2004) (Table 1).

The U.S. FDA approval for the venous leg ulcer was based on the manufacturer's randomised controlled trial (level II evidence) with 297 patients; 161 Apligraf[®] and 136 control patients (FDA, 2004b). The FDA based its assessment of effectiveness on results of only 240 patients

(130 Apligraf[®] and 130 control) due to concerns with clinical records at one of the participating centres. This study reported no difference in the overall closure rate of 55.4% (72/130) for Apligraf[®] and 49% (54/110) in the control group by 6 months (p=0.365).

Table 1 Adverse events and ulcer recurrence in diabetic foot ulcers by number of Apligraf[®] applications

Number of applications (number of patients)	Number of wounds closed (%)	Days to closure (range)	Number of first infections on study limb	Number of amputations on study limb	Number re-opened ≤ 4 weeks	Number re-closed by 6 months	Number re-opened by > 4 weeks	Number re-closed by 6 months
1 (n=10)	9/10 (90%)	15 (7-57)	1	0	4/9 (44%)	4/4	0/9	NA
2 (n=11)	8/11 (73%)	15 (8-36)	2	0	2/8 (25%)	2/2	1/8 (13%)	0/1
3 (n=15)	10/15 (67%)	22 (22-29)	5	0	4/10 (40%)	4/4	0/10	NA
4 (n=17)	9/17 (53%)	36 (29-78)	6	1	1/9 (11%)	0/1	1/9 (11%)	0/1
5 (n=59)	27/59 (46%)	51 (36-88)	24	6	11/27 (41%)	9/11	1/27 (4%)	1/1
Total Apligraf[®] Patients (n=112)	63 (56%)	36 (7-88)	38/112 (34%)	7	22/63 (35%)	19/22 (86%)	3/63 (5%)	1/3 (33%)
Total Control Patients (n=96)	36 (38%)	50 (15-92)	36/96 (38%)	15	13/36 (36%)	8/13 (62%)	3/36 (8%)	2/3 (67%)

COST IMPACT

The cost of Apligraf[®] is \$US 1115.00 per unit (email communication, Organogenesis 28th September, 2004). It is difficult to gauge the likely impact of Apligraf[®] without safety and effectiveness data in the long-term as all studies had a maximum follow-up of 6 months. The number of applications required will affect the total cost. It was not possible to access information on the cost of treating chronic venous leg ulcers in Australia.

An American economic assessment that compared Apligraf[®] to a compression boot for the treatment of hard-to-heal venous leg ulcers reported that the use of Apligraf[®] resulted in lower overall monthly treatment costs over one year (Schonfeld et al 2000). The cost analysis included primary therapeutic therapy, additional compression dressings, consultant visits, home visits, diagnostic tests and procedures, management of adverse events and hospitalisations.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The product material is cultured from foreskin removed in newborn circumcision.

CONCLUSION:

The quality of evidence for the use of Apligraf[®] is high, however it is potentially biased (level II evidence, without blinding). Although this evidence indicates limited benefit to patients in the long-term, there is a lack of studies comparing Apligraf[®] to alternative treatments. In addition, treatment with Apligraf[®] is costly.

HEALTHPACT ACTION:

As there are alternative therapies available in the Australian health system, it is therefore recommended that this technology be archived.

SOURCES OF FURTHER INFORMATION:

AIHW (2002). *Diabetes: Australian facts 2002* [Internet]. Australian Institute of Health and Welfare. Available from: <http://www.aihw.gov.au/publications/cvd/daf02/daf02-c04.pdf> [Accessed 5th August 2004].

Allie, D. E., Hebert, C. J. et al (2004). 'Novel treatment strategy for leg and sternal wound complications after coronary artery bypass graft surgery: Bioengineered Apligraf', *Ann Thorac Surg*, 78 (2), 673-678.

Bello, Y. M. & Falabella, A. F. (2002). 'The role of graftskin (Apligraf) in difficult-to-heal venous leg ulcers', *J Wound Care*, 11 (5), 182-183.

Brem, H., Kirsner, R. S. & Falanga, V. (2004). 'Protocol for the successful treatment of venous ulcers', *Am J Surg*, 188 (1A Suppl), 1-8.

Department Human Services, Victoria, 2004 [Internet] *Leg ulcers*: Available from: http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Leg_ulcers?open [Accessed 28th September, 2004].

Falanga, V. & Sabolinski, M. (1999). 'A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers', *Wound Repair Regen*, 7 (4), 201-207.

Fivenson, D. & Scherschun, L. (2003). 'Clinical and economic impact of Apligraf for the treatment of nonhealing venous leg ulcers', *Int J Dermatol*, 42 (12), 960-965.

Griffiths, M., Ojeh, N. et al (2004). 'Survival of apligraf in acute human wounds', *Tissue Eng*, 10 (7), 1180-1195.

Noel, B. (2001). 'Economic assessment of Apligraf for the treatment of venous leg ulcers', *Wound Repair Regen*, 9 (1), 60.

Organogenesis Inc. [Internet] *Organogenesis: What's New*. Available from: http://www.organogenesis.com/news/whats_new.asp#woundhealing [Accessed 29th September, 2004].

Schonfeld, W. H., Villa, K. F. et al (2000). 'An economic assessment of Apligraf (Graftskin) for the treatment of hard-to-heal venous leg ulcers', *Wound Repair Regen*, 8 (4), 251-257.

Shen, J. T. & Falanga, V. (2003). 'Innovative Therapies in Wound Healing', *J Cutan Med Surg*, April 22 [Epub ahead of print].

Sibbald, R. G., Torrance, G. W. et al (2001). 'Cost-effectiveness of Apligraf in the treatment of venous leg ulcers', *Ostomy Wound Manage*, 47 (8), 36-46.

United States Food and Drug Administration (2000) *Apligraf: Summary of Safety and Effectiveness Data*, [Internet] Available from: <http://www.fda.gov/cdrh/pdf/P950032S016b.pdf> [Accessed 22nd September, 2004].

United States Food and Drug Administration (1998) *Apligraf: Summary of Safety and Effectiveness Data*: [Internet] Available from: <http://www.fda.gov/cdrh/pdf/p950032.pdf> [Accessed 29th September, 2004]

SEARCH CRITERIA TO BE USED:

Leg Ulcer/ epidemiology/etiology/pathology/ therapy
Skin, Artificial
Varicose Ulcer/ therapy
Wound Healing