Caution: **Federal Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).**

1. DEVICE DESCRIPTION

Apligraf is a viable, bi-layered, skin construct: the epidermal layer is formed by human keratinocytes and has a well-differentiated stratum corneum; the dermal layer is composed of human fibroblasts in a bovine Type I collagen lattice. While matrix proteins and cytokines found in human skin are present in Apligraf, Apligraf does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles.

Apligraf is manufactured under aseptic conditions from human neonatal male foreskin tissue. The fibroblast and keratinocyte cell banks which are the source of the cells from which Apligraf is derived are tested for human and animal viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes and tumorigenicity. The final product is tested for morphology, cell viability, epidermal coverage, sterility, mycoplasma, and physical container integrity. Product manufacture also includes reagents derived from animal materials including bovine pituitary extract. All animal-derived reagents are tested for viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma before use and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE).

2. INTENDED USE / INDICATIONS

Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy.

3. CONTRAINDICATIONS

- Apligraf is contraindicated for use on clinically infected wounds.
- Apligraf is contraindicated in patients with known allergies to bovine collagen.
- Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium (Section 8).

4. WARNINGS

Warning: DO NOT OPEN AND DO NOT USE Apligraf after the expiration date or if the pH is not within the acceptable range (6.8-7.7) as determined by the provided color chart. (Section 9).

Warning: Allergic reactions to the components in the Apligraf agarose shipping medium (Section 8) and bovine collagen, (a component of Apligraf), have been reported. Discontinue product use if a patient shows evidence of an immunologic reaction. Patients should notify their physician of any symptoms of an allergic

reaction. In studies with 361 patients, no allergic reactions to Apligraf were reported.

5. PRECAUTIONS

Caution: Do not use Apligraf if there is evidence of container damage or product contamination.

Caution: Apligraf should not be reused, frozen or sterilized after opening.

Caution: Apligraf should be kept in its tray on the shipping medium in the sealed bag under controlled temperature (20-31°C) until ready for use.

Caution: Apligraf should be handled using sterile technique and placed on a prepared wound bed within 5 minutes of opening the package.

Caution: Do not use cytotoxic agents, including Dakin's solution, Mafenide Acetate, Scarlet Red Dressing, Tincoban, Zinc Sulfate, Povidone-iodine solution, or Chlorhexidine with Apligraf. In *in vitro* and *in vivo* histology studies, exposure to these agents degraded Apligraf. Device exposure to Mafenide acetate, Polymixin/Nystatin or Dakin's Solution also reduced Apligraf cell viability.

Caution: Diagnosis of wound infection may be complicated by the white or yellow appearance of Apligraf after it becomes hydrated with wound fluid. Apligraf-treated wounds with respect to signs of suspected infection, including a change from baseline at the ulcer site for pain, edema, erythema, drainage, odor, warmth and/or unexplained fever, should be evaluated and treated according to standard practice for infection.

Caution: The persistence of Apligraf cells on the wound and the safety of this device in venous ulcer patients beyond one year has not been evaluated. In clinical studies with Apligraf there have been no reports of long term sequelae associated with Apligraf use.

Caution: The safety and the effectiveness of Apligraf have not been established for patients receiving greater than 5 device applications.

6. ADVERSE EVENTS

All reported adverse events which occurred in the Apligraf cohort in the pivotal clinical study at an incidence of 1% or greater are listed in Table 1. The adverse events are listed in descending order according to frequency. This table lists all adverse events reported in the study including those attributed and not attributed to treatment.

Table 1
Adverse Events Reported in Greater than 1.0% of Apligraf Patients

	Apligraf (n = 161)	Control (n= 136)
	Total	Total
Suspected Wound Infection[1] (study site)	47 (29.2%)	19 (14.0%)
Suspected Wound Infection[1] (non-study site)	16 (9.9%)	15 (11.0%)
Cellulitis[2] (study site)	13 (8.1%)	11 (8.1%)
Cellulitis[2] (non-study site)	12 (7.5%)	7 (5.1%)
Dermatitis (non-study site)	10 (6.2%)	10 (7.4%)
Exudate (study site)	9 (5.6%)	0 (0.0%)
Peripheral Edema	8 (5.0%)	7 (5.1%)
Pain (study site)	7 (4.3%)	7 (5.1%)
Death	6 (3.7%)	6 (4.4%)
Skin Ulcer (non-study site)	6 (3.7%)	5 (3.7%)
Pain (non-study site)	5 (3.1%)	4 (2.9%)
Pruritus (non-study site)	5 (3.1%)	2 (1.5%)
Skin Ulcer (study site)	5 (3.1%)	3 (2.2%)
Infection (non-wound)	4 (2.5%)	1 (0.7%)
Positive Wound Culture[3] (study site)	4 (2.5%)	3 (2.2%)
Rhinitis	4 (2.5%)	1 (0.7%)
Dermatitis (study site)	4 (2.5%)	2 (1.5%)
Pain (overall body)	3 (1.8%)	2 (1.5%)
Congestive Heart Failure	3 (1.8%)	0 (0.0%)
Accidental Injury (musculoskeletal)	3 (1.8%)	0 (0.0%)
Dyspnea	3 (1.8%)	1 (0.7%)
Pharyngitis	3 (1.8%)	0 (0.0%)
Rash (study site)	3 (1.8%)	2 (1.5%)
Accidental Injury (overall body)	2 (1.3%)	1 (0.7%)
Asthenia	2 (1.3%)	0 (0.0%)
Arrhythmia	2 (1.3%)	0 (0.0%)
Abscess (non-study site)	2 (1.3%)	0 (0.0%)
Arthralgia	2 (1.3%)	2 (1.5%)
Cough Increased	2 (1.3%)	0 (0.0%)
Rash (non-study site)	2 (1.3%)	5 (3.7%)
Erythema (study site)	2 (1.3%)	1 (0.7%)
Kidney Failure	2 (1.3%)	0 (0.0%)
Urinary Tract Infection	2 (1.3%)	5 (3.7%)

In the clinical trial the following definitions were used:

[1]*Suspected Wound infection:* a wound with at least some clinical signs and symptoms of infection such as increased exudate, odor, redness, swelling, heat, pain, tenderness to the touch and purulent discharge; quantitative culture was not required.

[2]*Cellulitis:* a non-suppurative inflammation of the subcutaneous tissues extending along connective tissue planes and across intercellular spaces; widespread swelling, redness and pain without definite localization.

[3]*Positive wound culture:* reported as an adverse event, but not reported as a wound infection.

Adverse events were recorded as mild, moderate, severe or life-threatening. There were 1 life-threatening and 3 severe infections reported in the Apligraf group and none in the control arm. Of the four events, two severe infections were considered related to treatment: however one occurred one month after the last application of Apligraf and the other occurred following application on a pre-existing Pseudomonas infection.

7. CLINICAL STUDIES

Study Design - A prospective, randomized, controlled, multi-center, multi-specialty, unmasked study was conducted to evaluate the safety and effectiveness of Apligraf and compression therapy in comparison to an active treatment concurrent control of zinc paste gauze and compression therapy. The study population included consenting patients who were 18-88 years old, available for one year follow-up, with venous insufficiency confirmed by plethysmography (venous reflux < 20 sec.); associated with non-infected partial and / or full thickness skin loss ulcer (IAET Stage 2 or 3) of greater than one month duration and which had not adequately responded to conventional ulcer therapy. Patients were excluded for ankle brachial index < 0.65, severe rheumatoid arthritis, collagen vascular disease, pregnancy/lactation, cellulitis, osteomyelitis, ulcer with necrotic, avascular or bone/tendon/fascia exposed-bed, clinically significant wound healing impairment due to uncontrolled diabetes, or renal, hepatic, hematologic, neurologic or immune insufficiency or due to immunosuppressive agents such as corticosteroids (> 15 mg/day), radiation therapy or chemotherapy; or enrollment in studies within the past 30 days for investigational devices or within the past three months for investigational drugs related to wound healing.

Extremities with multiple ulcers were enrolled; however, only one ulcer per extremity was studied. Non-study ulcer care was not specifically defined. Study ulcer care was defined for the treatment (Apligraf and compression therapy) and control (zinc paste gauze and compression therapy), treatment groups in two phases:

1) Active Phase (0-8 weeks): All patients received: i) a non-adherent, ii) a non-occlusive and iii) a therapeutic compression dressing on day 0, mid-week during the first week (day 3-5), and at weeks 1-8. Control treated patients also received zinc impregnated gauze at each

visit. All Apligraf patients received Apligraf on day 0. At the day 3-5 and weeks 1, 2 and 3 visits, if less than 50% Apligraf take was observed, then patients received an additional application of Apligraf. Patients were not allowed to receive more than 5 Apligraf applications total.

2) Maintenance Phase (8-52 weeks): Closed-ulcer extremities received non-specified elastic compression stockings. Open-ulcer extremities continued with dressing changes.

Wound closure was defined as 100% epithelialization without drainage and assessed by clinical observation at visits on day 0, day 3-5, weekly from weeks 1-8, months 3 and 6 after initial treatment application or until wound closure was achieved. Additional follow-up visits were 9 and 12 months after initial treatment.

Study Results

The incidence of wound closure at set visits up to 6 months is presented below as the raw data results (Chart 1) and the results after adjustment for pooled center, baseline ulcer duration and baseline area (Chart 2).

Chart 1

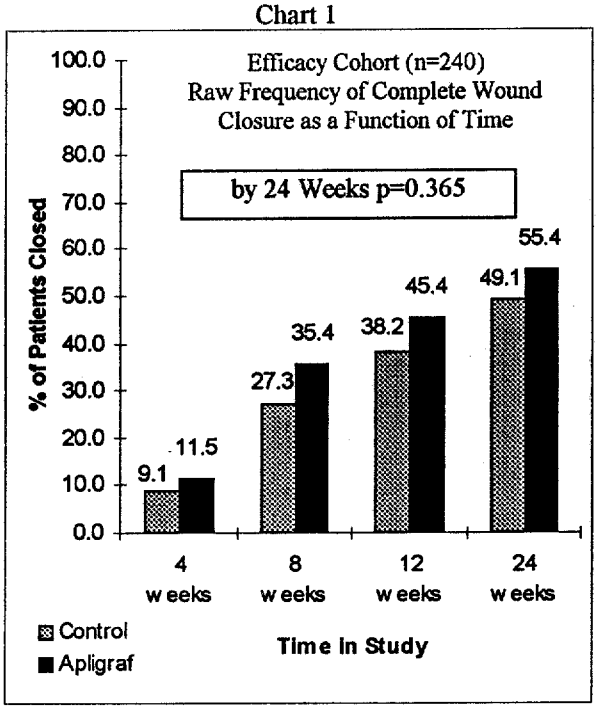
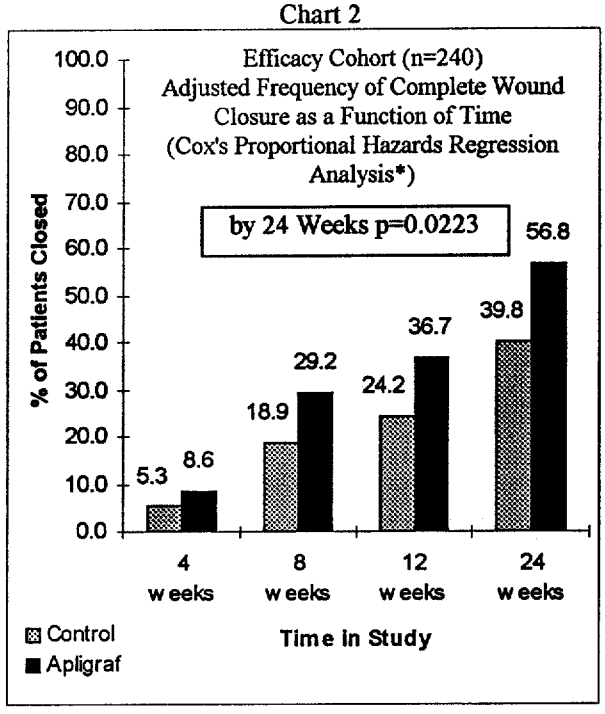


Chart 2



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Ulcer recurrence
At six months, the incidence of ulcer recurrence was 8.3% (6/72) for Apligraf- and 7.4% (4/54) for control-treated patients. The incidence of ulcer recurrence by 12 months was 18.1% (13/72) in the Apligraf group and 22.2% (12/54) in the control group.

Suspected wound infection
In the effectiveness cohort, there were 33/130 (25.4%) Apligraf-treated and 15/110 (13.6%) control-treated ulcers with suspected wound infection. While the overall incidence of wound infection was higher in the Apligraf arm, the incidence of wound closure (Charts 1 and 2) was also higher for Apligraf -treated patients.

Baseline status impact on wound closure
The impact of patient baseline status on wound closure was evaluated for the patient populations above and below the median values for ulcer duration and ulcer size as well as for baseline IAET Ulcer Stage, the presence of diabetes and a patient's Ankle Brachial Index. The results of these analyses are displayed in Table 2.

Table 2
Pre-Treatment Status and Wound Closure
Effectiveness Cohort (n=240 patients)

	Pre-Treatment Status		Number and Percent of Wound Closure by 6 months	
Patient Condition	No. and (%) Apligraf Pts.	No. and (%) Control Pts.	Apligraf	Control
Total	130 Patients	110 Patients	72 (55.4%)	54 (49.1%)
Ulcer Duration				
≤ 1 year	58 (44.6%)	62 (56.3%)	38/58 (65.5%)	45/62 (72.6%)
> 1 year	72 (55.4%)	48 (43.6%)	34/72 (47.2%)	9/48 (18.8%)
***Ulcer Area**				
< 500 mm^2	65 (50.0%)	60 (54.5%)	45/65 (69.2%)	35/60 (58.3%)
> 500 mm^2	63 (48.5%)	50 (45.5%)	26/63 (41.3%)	19/50 (38.0%)
IAET Staging				
Stage II	63 (48.5%)	56 (50.9%)	34/63 (54.0%)	32/56 (57.1%)
Stage III	67 (51.5%)	54 (49.1%)	38/67 (56.7%)	22/54 (40.7%)
Diabetes				
Yes[1]	25 (19.2%)	11 (10.0%)	12/25 (48.0%)	4/11 (36.4%)
No	105 (80.8%)	99 (90.0%)	60/105 (57.1%)	50/99 (50.5%)
****Ankle Brachial Index data (ABI)**				
> 0.65 - < 0.8	9 (6.9%)	10 (9.1%)	4/9 (44.4%)	4/10 (40.0%)
>0.8 - <1.0	43 (33.1%)	50 (45.5%)	26/43 (60.5%)	27/50 (54.0%)
>1.0	75 (57.7%)	49 (44.5%)	40/75 (53.3%)	22/49 (44.9%)

*Baseline ulcer area missing for two patients in the Apligraf group
**ABI data is missing for 3 Apligraf and 1 control patient
[1] This category includes both insulin-dependent and non-insulin dependent diabetes patients, because the insulin-dependence of patients was not determined in this clinical trial

Secondary Endpoints
Clinical assessment (scale 1-4) of wound depth (IAET staging), erythema, edema, wound pain, fibrin, exudate, granulation tissue and overall assessment by changes in mean score and analysis of variance from baseline to the 6 month visit indicated no differences between treatment groups at 6 months.

Immune response:
In tests of patients' sera there were no observations of antibody responses against bovine type I collagen, bovine serum proteins or the Class I HLA antigens on human dermal fibroblasts, and human epidermal cells. T-cell specific responses were also not observed against bovine type I collagen, human fibroblasts or human keratinocytes. There was also no clinical evidence of Apligraf rejection by any patient.

8. HOW SUPPLIED

Apligraf is supplied sealed in a heavy gauge polyethylene bag with a 10% CO_2/air atmosphere and agarose nutrient medium, ready for single use. To maintain cell viability, Apligraf should be kept in the sealed bag at 20-31°C until use. Apligraf is supplied as a circular disk approximately 75 mm in diameter and 0.75 mm thick. The agarose shipping medium contains agarose, L-glutamine, hydrocortisone/bovine serum albumin, bovine insulin, human transferrin, triiodothyronine, ethanolamine, O-phosphorylethanolamine, adenine, selenious acid, DMEM powder, HAM's F-12 powder, sodium bicarbonate, calcium chloride and water for injection.

To maintain cell viability, the product is aseptically manufactured, but not terminally sterilized. Apligraf is shipped following a preliminary sterility test with a 48 hour incubation to determine the absence of microbial growth. Final (14 day incubation) sterility tests results are not available at the time of application.

9. DIRECTIONS FOR USE

Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf consists of living cells which must be kept sealed in its nutrient medium and 10% CO_2/air atmosphere under controlled temperature (20-31° C) and used within 5 minutes of opening.

Preparation of the Venous Ulcer Wound Bed Prior to Apligraf Application

1. **Wound Infection:**
   Apligraf should not be applied over infected or deteriorating wounds until the underlying condition has been resolved.

2. **Bacterial containment:**
   Antimicrobial agents may be used during the week prior to Apligraf application to reduce the risk of infection. Dakin's solution, Mafenide Acetate, Scarlet Red Dressing, Tincoban, Zinc Sulfate, Povidone-iodine solution, and Chlorhexidine have been determined to be cytotoxic to Apligraf.

3. **Wound bed preparation:**
   Apligraf should be applied to a clean, debrided wound after thoroughly irrigating the wound with a non-cytotoxic solution. Oozing or bleeding resulting from debridement should be stopped through the use of gentle pressure. Previous ulcer treatments other than standard therapeutic compression should be discontinued.

4. **Control of Heavy Exudation:**
   Heavy exudation may displace Apligraf and reduce adherence. Exudation should be minimized by appropriate clinical treatment. If exudation persists, Apligraf should be made permeable to exudate by perforating the Apligraf to allow for drainage.

Suggested Technique for the Application of Apligraf to the Wound

1. Check expiration date. If expired, do not open or use.
2. Check product pH. If not 6.8-7.7 by the provided color pH chart, do not open or use.
3. Prepare a sterile field and atraumatic instruments: forceps.
4. Cut open the sealed polyethylene bag and transfer the plastic tray to the sterile field with aseptic technique.
5. Lift off the tray lid and note epidermal and dermal layer orientation: Apligraf is packaged with the epidermal (dull, mattte finish) layer facing up and the dermal (glossy) layer facing down.
6. Using the sterile atraumatic instrument, gently dislodge approximately 0.5 inch of Apligraf away from the wall of the tray.
7. With sterile gloved hands, insert one index finger under the released section of Apligraf. Use the other index finger to grasp the Apligraf in a second spot along the edge of the device. Holding the Apligraf in two places lift the entire Apligraf out of the tray using a smooth, even motion. This easy motion should prevent Apligraf from bending and folding

over onto itself. To minimize Apligraf damage: avoid Apligraf contact with foreign bodies and minimize handling Apligraf except by its margins.

8. Do not allow Apligraf to fold or wrinkle on itself. If excessive folding occurs, Apligraf can be floated (epidermal surface up) onto warm sterile saline solution in a sterile tray.

9. Apligraf should be placed such that the dermal layer (the glossy layer closest to the medium) is in direct contact with the wound surface. Trim Apligraf so as to cover the wound bed with 1/8 -1/4" margins.

10. Secure Apligraf with a three layer dressing so as to assure contact to wound bed:

    - Apply a non-adherent dressing over the ulcer and Apligraf, extending 0.5 inch beyond the ulcer perimeter and inflamed skin margins.
    - Apply a non-occlusive dressing such as fine mesh gauze. This may be folded or rolled as a bolster.
    - Apply a self adherent elastic wrap from metatarsals to tibial plateau so that therapeutic compression is applied to the ulcer site.

Frequency of Dressing Changes and Apligraf Applications

1. The wound should be inspected and the dressing changed at least once a week during the immediate post application period. More frequent changes may be required on highly exudative wounds.
2. Additional applications of Apligraf may be necessary. Prior to additional applications, non-adherent remnants of Apligraf should be gently removed. Healing tissue or adherent Apligraf should not be disrupted. The wound bed should be cleansed with a non-cytotoxic solution prior to additional applications of Apligraf. Additional applications of Apligraf should not be applied over areas where Apligraf is adherent.
3. The wound site should continue to be dressed with a non-adherent dressing, pressure bolster and elastic overwrap as described above.
4. Upon complete wound closure, patients should be continued with compression therapy such as support stockings.
5. The safety and the effectiveness of Apligraf have not been established for patients receiving greater than 5 device applications.

10. PATIENT'S MANUAL

A brochure will be made available to:
1. Provide basic information about chronic wounds.
2. Address standard patient care while receiving Apligraf treatment
3. Educate patients on Apligraf-related healing process.

11. PEEL-OFF LABEL

Remove the peel-off label from the lower right corner of the Apligraf package label and place it in the patient's chart. This label bears a unique lot number and expiration date of the Apligraf.

Organogenesis Inc., APLIGRAF (Graftskin)
Essential Prescribing Information
Numbers in parentheses ( ) refer to sections in the main part of the product labeling

Device Description
Apligraf is a bi-layered viable skin construct manufactured using neonatal foreskin keratinocytes and fibroblasts with bovine Type I collagen. **(1)**

Intended Use/Indications
Apligraf is indicated for use with standard therapeutic compression in the treatment of uninfected partial and/or full-thickness skin loss ulcers due to venous insufficiency and of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. **(2)**

Contraindications
Apligraf is contraindicated for use on clinically infected wounds and in patients with known allergies to bovine collagen or hypersensitivity to the components of the shipping medium.**(3, 4, 5, 8)**

Warnings and Precautions
If the expiration date or product pH is not within the acceptable range (6.8-7.7) DO NOT OPEN AND DO NOT USE the product. A clinical determination of wound infection should be made based on all of the signs and symptoms of infection. **(4, 5)**

Adverse Events
In the controlled clinical study conducted in patients with ulcers due to venous insufficiency of greater than one month in duration, suspected infection was reported more frequently in Apligraf-treated (29.2%) than control patients (14.0%). There were 1 life-threatening and 3 severe infections in the Apligraf group and none in the control arm. Of these, two severe infections were considered related to treatment: however one occurred one month after the last application of Apligraf and the other occurred following application on a pre-existing Pseudomonas infection.

While the overall incidence of wound infection was higher in the Apligraf arm, the incidence of wound closure was 72/130 (55.4%) and 54/110 (49.1%) for Apligraf and Control treated patients, respectively. **(6)**

Maintaining Device Effectiveness
Apligraf has been processed under aseptic conditions and should be handled observing sterile technique. It should be kept in its tray on the medium in the sealed bag under controlled temperature (20-31°C) until ready for use. Apligraf should be placed on the wound bed within 5 minutes of opening the package. Handling before application to the wound site should be minimal. If there is any question that Apligraf may be contaminated or compromised, it should not be used. Apligraf should not be used beyond the listed expiration date.(9)

Use in Specific Populations
The safety and effectiveness of Apligraf has not been established in pregnant women, acute wounds, burns and ulcers caused by diabetic neuropathy or pressure.

Patient Counseling Information
Patients should be counseled regarding the importance of complying with compression therapy or other treatment which may be prescribed in conjunction with Apligraf.

How Supplied
Apligraf is supplied sealed in a heavy gauge polyethylene bag with a 10% CO_2/air atmosphere and agarose nutrient medium, ready for single use. To maintain cell viability, Apligraf should be kept in the sealed bag at 20-31°C until use. Apligraf is supplied as a circular disk approximately 75 mm in diameter and 0.75 mm thick.