

# Organogenesis<sup>inc.</sup>

LIVING TECHNOLOGY



 ***Dermagraft***<sup>®</sup>  
*Human fibroblast-derived  
dermal substitute*

DIRECTIONS FOR USE

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CAUTION: Federal (U.S.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

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## 1. DEVICE DESCRIPTION

Dermagraft® is a cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold.

Dermagraft is manufactured from human fibroblast cells derived from donated newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles.

The human fibroblast cells are from a qualified cell bank, which has been extensively tested for animal viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity. Reagents used in the manufacture of Dermagraft are tested and found free from viruses, retroviruses, endotoxins, and mycoplasma before use. Dermagraft is manufactured with sterile components under aseptic conditions within the final package.

Prior to release for use, each lot of Dermagraft must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability. Maternal blood sera testing for evidence of infection with human immunodeficiency virus type 1 (HIV-1), human immunodeficiency virus type 2 (HIV-2), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, human T-lymphotropic virus type 1 (HTLV-1)

was coordinated by an FDA registered laboratory in accordance with the Clinical Laboratory Improvement Amendments. These test results were found negative for the purposes of donor selection and found suitable by Organogenesis Inc. During subsequent screening of the fibroblast master cell bank, testing for these same viruses, as well as HTLV-2 and Epstein-Barr virus (EBV) is carried out and found to be negative.

Dermagraft® is supplied frozen in a clear bag containing one piece of approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application.

## 2. INTENDED USE/INDICATIONS

Dermagraft is indicated for use in the treatment of full-thickness diabetic foot ulcers greater than six weeks duration, which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure. Dermagraft should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot.

### 3. CONTRAINDICATIONS

Dermagraft® is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts.

Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution.

### 4. WARNINGS

None

### 5. PRECAUTIONS

**CAUTION:** Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on an ulcer being treated with Dermagraft as such preparations may cause reduced viability of Dermagraft.

**CAUTION:** To ensure the delivery of metabolically active, living cells to the patient's wound, do not hold Dermagraft at room temperature for more than 30 minutes. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation for Use instructions.

**CAUTION:** The persistence of Dermagraft in the wound and the safety of this device in diabetic foot ulcer patients beyond six months has not been evaluated. Testing has not revealed a tumorigenic potential for cells contained in the device. However, the long-term response to these cells is unknown.

**CAUTION:** Do not use the product if there is evidence of container damage or if the date and time stamped on the shipping box has expired.

CAUTION: Do not reuse, refreeze, or sterilize the product or its container.

CAUTION: Always thaw and rinse product according to the Preparation for Use instructions to ensure the delivery of metabolically active, living cells to the patient's wound.

CAUTION: Dermagraft® is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided.

CAUTION: Do not use Dermagraft after the expiration date indicated on the labeled unit carton.

CAUTION: The product must remain frozen at  $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$  continuously until ready for use.

CAUTION: Dermagraft has not been studied in patients receiving greater than 8 device applications.

CAUTION: Dermagraft has not been studied in patients with wounds that extend into the tendon, muscle, joint capsule, or bone. Dermagraft has not been studied in children under the age of 18 years, in pregnant women, in patients with ulcers over a Charcot deformity of the mid-foot, or in patients receiving corticosteroids or immunosuppressive or cytotoxic agents.

## 6. ADVERSE EVENTS

A total of 695 patients were evaluated in four clinical trials, 389 treated with Dermagraft, and 306 treated with Control. Adverse events that were reported in the pivotal 314-patient clinical trial at a frequency of greater than 1% for patients treated with Dermagraft are presented in Table 1. Adverse Event data are also presented combined, from three previous studies.

**TABLE 1 - ADVERSE EVENTS REPORTED IN GREATER THAN 1% OF PATIENTS TREATED WITH DERMAGRAFT®**

| Event  | Pivotal Study                |                           | Previous Studies             |                           |
|--|------------------------------|---------------------------|------------------------------|---------------------------|
|  | Dermagraft<br>N=163<br>n (%) | Control<br>N=151<br>n (%) | Dermagraft<br>N=226<br>n (%) | Control<br>N=155<br>n (%) |
| Infection (study wound) <sup>1</sup>           | 17 (10.4)                    | 27 (17.9)                 | 63 (27.9)                    | 43 (27.7)                 |
| Infection (non-study wound)                    | 17 (10.4)                    | 14 (9.3)                  | 33 (14.6)                    | 22 (14.2)                 |
| Accidental injury <sup>2</sup>                 | 17 (10.4)                    | 18 (11.9)                 | 17 (7.5)                     | 11 (7.1)                  |
| Skin dysfunction/Blister                       | 16 (9.8)                     | 20 (13.2)                 | 38 (16.8)                    | 31 (20.0)                 |
| Flu syndrome                                   | 15 (9.2)                     | 9 (6.0)                   | 7 (3.1)                      | 8 (5.2)                   |
| Osteomyelitis (study wound)                    | 14 (8.6)                     | 13 (8.6)                  | 17 (7.5)                     | 8 (5.2)                   |
| Surgeries involving study ulcer <sup>3</sup>   | 13 (8.0)                     | 21 (13.9)                 | 35 (15.5)                    | 13 (8.4)                  |
| Wound enlargement/Skin ulcer (non-study wound) | 12 (7.4)                     | 17 (11.3)                 | 30 (13.3)                    | 16 (10.3)                 |
| Cellulitis (study wound)                       | 12 (7.4)                     | 14 (9.3)                  | 25 (11.1)                    | 10 (6.5)                  |
| Cellulitis (non-study wound)                   | 10 (6.1)                     | 7 (4.6)                   | 15 (6.6)                     | 13 (8.4)                  |
| Peripheral edema/<br>Localized swelling        | 9 (5.5)                      | 7 (4.6)                   | 20 (8.8)                     | 6 (3.9)                   |
| Pharyngitis/URI                                | 7 (4.3)                      | 5 (3.3)                   | 13 (5.8)                     | 11 (7.1)                  |
| Pain   | 6 (3.7)                      | 5 (3.3)                   | 24 (10.6)                    | 12 (7.7)                  |
| Lab test abnormal - chemistry <sup>4</sup>     | 6 (3.7)                      | 5 (3.3)                   | 37 (16.4)                    | 31 (20.0)                 |
| Skin disorder <sup>5</sup>                     | 5 (3.1)                      | 4 (2.6)                   | 0 (0.0)                      | 0 (0.0)                   |
| Osteomyelitis (non-study wound)                | 5 (3.1)                      | 2 (1.3)                   | 10 (4.4)                     | 6 (3.9)                   |
| Wound enlargement/<br>Skin ulcer (study wound) | 4 (2.5)                      | 8 (5.3)                   | 12 (5.3)                     | 15 (19.7)                 |
| Urinary tract infection                        | 4 (2.5)                      | 1 (0.7)                   | 7 (3.1)                      | 6 (3.9)                   |
| Diarrhea                                       | 4 (2.5)                      | 5 (3.3)                   | 4 (1.8)                      | 3 (1.9)                   |
| Rash   | 3 (1.8)                      | 2 (1.3)                   | 4 (1.8)                      | 4 (2.6)                   |
| Myocardial infarct                             | 3 (1.8)                      | 0 (0.0)                   | 0 (0.0)                      | 4 (2.6)                   |
| Fever  | 3 (1.8)                      | 0 (0.0)                   | 8 (3.5)                      | 3 (1.9)                   |
| Allergic reaction                              | 3 (1.8)                      | 1 (0.7)                   | 1 (0.4)                      | 1 (0.6)                   |
| Rhinitis                                       | 2 (1.2)                      | 1 (0.7)                   | 2 (0.9)                      | 2 (1.3)                   |
| Nail disorder                                  | 2 (1.2)                      | 3 (2.0)                   | 1 (0.4)                      | 3 (1.9)                   |
| Myalgia  | 2 (1.2)                      | 0 (0.0)                   | 0 (0.0)                      | 0 (0.0)                   |
| Joint disorder                                 | 2 (1.2)                      | 1 (0.7)                   | 1 (0.4)                      | 0 (0.0)                   |
| Headache                                       | 2 (1.2)                      | 1 (0.7)                   | 3 (1.3)                      | 3 (1.9)                   |
| Gastrointestinal disorder                      | 2 (1.2)                      | 3 (2.0)                   | 0 (0.0)                      | 1 (0.6)                   |

**TABLE 1 (CONT.) - ADVERSE EVENTS REPORTED IN GREATER THAN 1% OF PATIENTS TREATED WITH DERMAGRAFT®**

| Event                          | Pivotal Study                |                           | Previous Studies             |                           |
|--------------------------------|------------------------------|---------------------------|------------------------------|---------------------------|
|                                | Dermagraft<br>N=163<br>n (%) | Control<br>N=151<br>n (%) | Dermagraft<br>N=226<br>n (%) | Control<br>N=155<br>n (%) |
| Chest pain                     | 2 (1.2)                      | 1 (0.7)                   | 4 (1.8)                      | 5 (3.2)                   |
| Anemia                         | 2 (1.2)                      | 0 (0.0)                   | 4 (1.8)                      | 0 (0.0)                   |
| Bronchitis                     | 1 (0.6)                      | 1 (0.7)                   | 7 (3.1)                      | 1 (0.6)                   |
| Eccymosis                      | 1 (0.6)                      | 0 (0.0)                   | 5 (2.2)                      | 0 (0.0)                   |
| Sinusitis                      | 1 (0.6)                      | 0 (0.0)                   | 4 (1.8)                      | 3 (1.9)                   |
| Neuropathy                     | 1 (0.6)                      | 0 (0.0)                   | 4 (1.8)                      | 0 (0.0)                   |
| Nausea                         | 1 (0.6)                      | 2 (1.3)                   | 4 (1.8)                      | 1 (0.6)                   |
| Dyspnea                        | 1 (0.6)                      | 1 (0.7)                   | 4 (1.8)                      | 0 (0.0)                   |
| Vomiting                       | 1 (0.6)                      | 1 (0.7)                   | 3 (1.3)                      | 2 (1.3)                   |
| Sepsis/Septicemia              | 1 (0.6)                      | 1 (0.7)                   | 3 (1.3)                      | 0 (0.0)                   |
| Gastroenteritis                | 1 (0.6)                      | 0 (0.0)                   | 3 (1.3)                      | 1 (0.6)                   |
| Chills                         | 1 (0.6)                      | 0 (0.0)                   | 3 (1.3)                      | 3 (1.9)                   |
| Cataract                       | 1 (0.6)                      | 0 (0.0)                   | 3 (1.3)                      | 1 (0.6)                   |
| Angina pectoris                | 1 (0.6)                      | 0 (0.0)                   | 3 (1.3)                      | 3 (1.9)                   |
| Wound drainage                 | 0 (0.0)                      | 0 (0.0)                   | 11 (4.9)                     | 5 (3.2)                   |
| Cerebrovascular accident       | 0 (0.0)                      | 0 (0.0)                   | 7 (3.1)                      | 1 (0.6)                   |
| Congestive heart failure       | 0 (0.0)                      | 3 (2.0)                   | 6 (2.7)                      | 1 (0.6)                   |
| Cough increased                | 0 (0.0)                      | 2 (1.3)                   | 5 (2.2)                      | 2 (1.3)                   |
| Back pain                      | 0 (0.0)                      | 1 (0.7)                   | 5 (2.2)                      | 4 (2.6)                   |
| Peripheral vascular disorder   | 0 (0.0)                      | 0 (0.0)                   | 4 (1.8)                      | 0 (0.0)                   |
| Retinal disorder/Retinopathy   | 0 (0.0)                      | 0 (0.0)                   | 3 (1.3)                      | 1 (0.6)                   |
| Neoplasm <sup>5</sup>          | 0 (0.0)                      | 0 (0.0)                   | 3 (1.3)                      | 1 (0.6)                   |
| Lab test abnormal - urinalysis | 0 (0.0)                      | 0 (0.0)                   | 3 (1.3)                      | 2 (1.3)                   |
| Cyst                           | 0 (0.0)                      | 0 (0.0)                   | 3 (1.3)                      | 1 (0.6)                   |
| Asthenia                       | 0 (0.0)                      | 0 (0.0)                   | 3 (1.3)                      | 0 (0.0)                   |

- 1 Infections include all local wound infections, regardless of etiology (e.g., bacterial, fungal), not including osteomyelitis and cellulitis.
- 2 Examples of verbatim codes included in this category are: laceration, foreign body in eye, head injury, dislocation of hip, coccyx fracture post fall, skin tear, and burn right index finger.
- 3 Surgical procedures to the study ulcer are defined as any procedure (i.e., surgical debridement more extensive than required by protocol, incision and drainage, revision, excision, or amputation) that occurred during the course of the study.
- 4 Pilot study codes to "Lab Tests Abnormal" and does not distinguish between Chemistry, Hematology, and Urinalysis.
- 5 None of the events reported under "Skin disorder" involved the study ulcer. Under "Neoplasm", none of the events reported involved the study leg for the DERMAGRAFT-treated patients.

## 7. CLINICAL STUDY

The pivotal study was a multi-center, controlled randomized clinical trial in which 314 patients were treated with either Dermagraft® plus conventional therapy or conventional therapy alone (sharp debridement, saline-moistened gauze, and pressure-reducing footwear). Patients were eligible to be screened if they had a plantar diabetic foot ulcer on the heel or forefoot (including toes) that was  $\geq 1 \text{ cm}^2$  and  $\leq 20 \text{ cm}^2$ . At the screening visit, the patients began treatment with sharp debridement and saline-moistened gauze. If the study ulcer had not decreased in size by more than 50% during the next 2 weeks and the patient met all other inclusion and exclusion criteria, the patient was randomized into the study. Key study exclusion criteria included the following: a) the Ankle-Arm Index on the study foot was  $<0.7$ ; b) the study ulcer was over a Charcot deformity of the mid-foot; c) the study ulcer had sinus tracts or tunnels that could not be completely debrided; d) the study ulcer had increased or decreased in size by  $>50\%$  during the two week screening period; e) the patient had a serum albumin  $<2.0\text{g/dl}$ ; f) the patient was receiving corticosteroids or immunosuppressive or cytotoxic agents; and g) the study ulcer showed clinical signs of infection.

Except for the application of Dermagraft, treatment of study ulcers was identical for patients in both the Dermagraft and Control groups. Patients in the Dermagraft group received up to 8 applications of Dermagraft over the course of the 12-week study. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. Total off-weighting (e.g., use of crutches and wheelchairs) was not required by the study protocol.



Patients were followed weekly until their study wounds were confirmed healed or they completed the week 12 study visit. At the weekly study visits, ulcer tracings were obtained for computer planimetry and photographs of the wounds were taken as a pictorial record of the study ulcer.

The primary endpoint for the pivotal study was complete wound closure by week 12. Wound closure was defined as full epithelialization without drainage. Furthermore, a determination of wound closure was only made if the wound remained closed at a second, confirmatory visit occurring within 4 weeks of the first assessment of closure. If the wound was not healed at the confirmatory visit, the wound was not deemed closed.

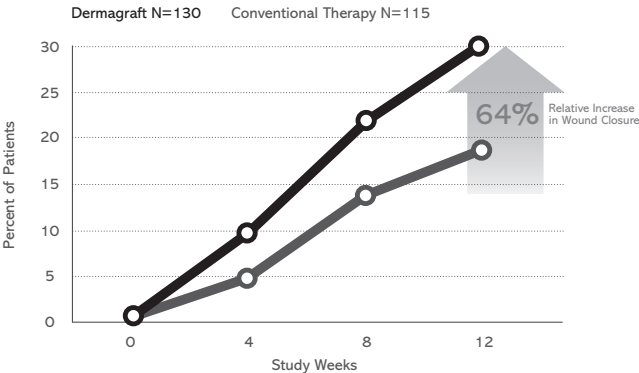
A planned interim analysis was performed during the study that showed a relationship between ulcer duration at the time of screening and incidence of ulcer healing with Dermagraft®. Consequently, a modified (after the interim analysis) statistical plan specified that (1) the effectiveness analyses would be based only on the patients with ulcers greater than 6 weeks duration at the time of the screening visit and (2) the primary endpoint would be analyzed using Bayesian statistical methods. Bayesian methods provide for information obtained during the initial part of a trial to be utilized prospectively in the latter part of the trial to enable overall estimation of measures of effectiveness. The effectiveness data are therefore based on the 245 patients with ulcers of greater than 6 weeks duration. The safety analyses were performed on all 314 patients who were randomized into the study.

The Bayesian analysis concluded that the probability that Dermagraft plus conventional therapy increased the chance of achieving wound closure in patients with ulcers greater than 6 weeks duration over and above that of conventional therapy alone was 98.4%. Furthermore, there

is a 95% probability that the chance of achieving closure in patients with ulcers greater than 6 weeks duration ranges from 22% to 38% in the Dermagraft® group and 12% to 26% in the Control group.

FIGURE 1 presents the proportion of patients who achieved complete wound closure during the course of the study.

FIGURE 1 - Complete Wound Closure for Ulcers of Greater Than 6 Weeks Duration for DERMAGRAFT (N=130) and Conventional Therapy (N=115).



Patients reported being ambulatory an average of 8 hours per day.

Patient characteristics, demographics, and healing results by patient category are provided in Table 2.

**TABLE 2 - SUMMARY OF COMPLETE WOUND CLOSURE RESULTS BY PATIENT CATEGORY FOR PATIENTS WITH WOUNDS OF GREATER THAN 6 WEEKS DURATION<sup>1</sup>**

| Category  | Number and Percent of Wound Closure by 12 Weeks |                                 |
|---|---|---------------------------------|
|   | Dermagraft <sup>a</sup><br>n/N (%) <sup>2</sup> | Control<br>n/N (%) <sup>2</sup> |
| <b>Age (years)<sup>3</sup></b>                        |   |                                 |
| ≤55   | 17/65 (26.2)                                    | 14/63 (22.2)                    |
| >55   | 22/65 (33.8)                                    | 7/52 (13.5)                     |
| <b>Albumin (g/dL)<sup>3</sup></b>                     |   |                                 |
| ≤4.0  | 24/70 (34.3)                                    | 12/67 (17.9)                    |
| >4.0  | 14/59 (23.7)                                    | 9/48 (18.8)                     |
| <b>Alcohol Use</b>                                    |   |                                 |
| Yes   | 6/37 (16.2)                                     | 5/28 (17.9)                     |
| No  | 33/93 (35.5)                                    | 16/87 (18.4)                    |
| <b>Ankle-Arm Index<sup>3</sup></b>                    |   |                                 |
| ≤1.1  | 20/70 (28.6)                                    | 12/54 (22.2)                    |
| >1.1  | 18/58 (31.0)                                    | 9/60 (15.0)                     |
| <b>Body Mass Index (kg/m<sup>2</sup>)<sup>3</sup></b> |   |                                 |
| ≤31.1   | 21/68 (30.9)                                    | 14/55 (25.4)                    |
| >31.1   | 18/62 (29.0)                                    | 7/60 (11.7)                     |
| <b>Diabetes Type</b>                                  |   |                                 |
| Type I  | 8/32 (25.0)                                     | 5/27 (18.5)                     |
| Type II   | 31/98 (31.6)                                    | 16/88 (18.2)                    |
| <b>Gender</b>   |   |                                 |
| Male  | 22/90 (24.4)                                    | 15/91 (16.5)                    |
| Female  | 17/40 (42.5)                                    | 6/24 (25.0)                     |
| <b>Hemoglobin A1c (%)<sup>3</sup></b>                 |   |                                 |
| ≤8.5  | 19/65 (29.2)                                    | 13/58 (22.4)                    |
| >8.5  | 20/64 (31.2)                                    | 8/56 (14.3)                     |
| <b>Mean Hours Non-Weight Bearing<sup>3</sup></b>      |   |                                 |
| ≤15.7   | 15/54 (27.8)                                    | 13/58 (22.4)                    |
| >15.7   | 21/65 (32.3)                                    | 7/47 (14.9)                     |
| <b>Number of Ulcers on Study Foot</b>                 |   |                                 |
| 1   | 37/126 (29.4)                                   | 20/108 (18.5)                   |
| >1  | 2/4 (50.0)                                      | 1/7 (14.3)                      |
| <b>Race</b>   |   |                                 |
| Caucasian   | 27/90 (30.0)                                    | 16/87 (18.4)                    |
| Non-Caucasian   | 12/40 (30.0)                                    | 5/28 (17.9)                     |
| <b>Smoker</b>   |   |                                 |
| Yes   | 8/27 (29.6)                                     | 4/17 (23.5)                     |
| No  | 31/103 (30.1)                                   | 17/98 (17.3)                    |
| <b>Ulcer Area (cm<sup>2</sup>)<sup>3</sup></b>        |   |                                 |
| ≤1.5  | 24/60 (40.0)                                    | 15/63 (23.8)                    |
| >1.5  | 15/70 (21.4)                                    | 6/52 (11.5)                     |
| <b>Ulcer Location</b>                                 |   |                                 |
| Forefoot or Toe                                       | 33/112 (29.5)                                   | 20/102 (19.6)                   |
| Heel  | 6/18 (33.3)                                     | 1/13 (7.7)                      |

1 Data observed at Screening except for Ulcer Area (obtained at the day 0 randomization visit) and Mean Hours Non-Weight Bearing (compiled from patient diary information received from Study Weeks 1 through Termination; patients were included if they turned in at least one diary from any post randomization visit).

2 Note: For individual categories the N will vary based on available patient information.

3 Cut-off values for each category are based on the overall median value.

The healing results presented in Table 2 are presented for general information purposes only. Outcome data based on an analysis of one demographic parameter in isolation may not be predictive of wound closure, as multiple factors influence ulcer healing.

**TABLE 3 - SUMMARY OF COMPLETE WOUND CLOSURE RESULTS BY ULCER DURATION**

| Ulcer Duration        | Number and Percent of Wound Closure by 12 Weeks |                    |
|-----------------------|---|--------------------|
|                       | Dermagraft®<br>n/N (%)                          | Control<br>n/N (%) |
| <6 weeks <sup>1</sup> | 13/33 (39.0)                                    | 15/36 (42.0)       |
| 6-26 weeks            | 19/68 (27.9)                                    | 11/55 (20.0)       |
| >26 weeks             | 20/62 (32.3)                                    | 10/60 (16.7)       |

<sup>1</sup>These 69 patients with ulcers less than 6 weeks duration were not included in the primary effectiveness analysis.

## RECURRENCE

In the previous multi-center controlled trial 139 patients were treated with Dermagraft and 142 patients were treated with control. All patients were followed to week 32. Ulcer recurrence (defined as ulcers that healed by week 12 and reopened on or before week 32) was 26% (11/42) for patients in the Dermagraft group and 22% (9/41) for patients in the Control group. Among this group of patients that experienced recurrence, the median time from healing to recurrence was 10 weeks for the Dermagraft group, and 7 weeks for the Control group. These results are reflective of the entire study population, regardless of ulcer duration, and include patients who received Dermagraft that did not meet the final metabolic release criterion.

After this study was completed, the metabolic release criterion for Dermagraft and the intended patient population were modified. Therefore, a retrospective analysis was also performed on a subset of patients with ulcer duration of greater than 6 weeks who received

Dermagraft® that met the final metabolic release criterion versus Control patients with ulcer duration of greater than 6 weeks. Ulcer recurrence was 18.8% (3/16) for patients in the Dermagraft group and 20.7% (6/29) for patients in the Control group.

## **IMMUNOLOGY AND PERSISTENCE STUDIES**

The potential for Dermagraft to elicit an immune response was evaluated by examining the baseline and terminal sera of patients enrolled in a clinical trial for Dermagraft using Western Blot technique. A comparison of pre- and post-immune sera did not indicate an immunologic response to Dermagraft in patients treated with up to 8 pieces of Dermagraft. In investigating the persistence of the product in the wound bed, testing using Y-chromosome (male donor) marker SRY, amplified by a nested PCR technique revealed the presence of cells from Dermagraft in biopsies of treated venous ulcers up to 6 months after treatment from a single piece of Dermagraft. Six of 10 patients evaluated at 2 months demonstrated DNA from cells from Dermagraft. Three of 10 patients evaluated at 6 months demonstrated DNA from cells from Dermagraft. In addition, biopsies of these wounds were evaluated for histologic evidence of an immunologic response to the product. This assessment found no histologic changes suggestive of an immune response to Dermagraft.

## 8. PATIENT COUNSELING INFORMATION

After implantation of Dermagraft<sup>®</sup>, patients should be instructed not to disturb the ulcer site for approximately 72 hours (three days). After this time period, the patient, or caregiver, should perform the first dressing change. The frequency of additional dressing changes should be determined by the treating physician. Patients should be given detailed instructions on proper wound care so they can manage dressing changes between visits. Compliance with off weight-bearing instructions should be emphasized.

Patients should be advised that they are expected to return for follow-up treatments on a routine basis, until the ulcer heals or until they are discharged from treatment. Patients should be instructed to contact their physician, if at any time they experience pain or discomfort at the ulcer site or if they notice redness, swelling, or discharge around/from the ulcer.

## 9. HOW SUPPLIED

Dermagraft is supplied frozen in a clear bag containing one piece of approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application. The clear bag is enclosed in a foil pouch and labeled unit carton.

**CAUTION:** Dermagraft is limited to single-use application. Do not reuse, refreeze, or sterilize the product or its container.

Dermagraft is manufactured using sterile components and is grown under aseptic conditions. Prior to release for use, each lot of Dermagraft must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability.

Dermagraft® is grown on a bioabsorbable mesh. The mesh provides a three-dimensional scaffolding to facilitate cell growth and tissue formation during the manufacturing process. For clinical application, the mesh must retain its integrity only until the tissue is delivered to the wound bed. Dermagraft detached from welds within the pouch does not compromise either the safety or efficacy of Dermagraft.

Dermagraft is packaged with a saline-based cryoprotectant. This solution is supplemented with 10% DMSO (Dimethylsulfoxide) and bovine serum to facilitate long-term frozen storage of the product. Skin and eye contact with this packaging solution should be avoided. Refer to the step-wise thawing and rinsing procedures to ensure delivery of a metabolically active product to the wound bed.

## 10. STORAGE

Dermagraft must be stored continuously at  $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . For continuous storage, the transfer of Dermagraft from its original shipping container into an appropriate freezer must take no longer than 15 seconds to ensure cell viability.

## 11. SHELF LIFE

The unit carton containing Dermagraft is marked with the expiration date of the product. Do not use the product after this date.

## 12. PEEL-OFF LABEL

Two peel-off labels are provided on the box containing Dermagraft. One of the peel-off labels should be removed and placed on the patient's chart. This label bears a unique lot number and expiration date that facilitates the collection of product monitoring information.

## 13. DIRECTIONS FOR USE

In clinical studies evaluating Dermagraft for the treatment of ulcers in diabetic patients, Dermagraft was applied weekly for up to a total of 8 applications over a 12-week period.

### **APPLICATION NOTES**

- Diabetic foot ulcers must receive adequate sharp debridement, removing any necrotic or hyperkeratinized tissue, leaving a wound bed that meets the clinical criteria for skin grafting prior to application of Dermagraft® (i.e., clean, granulating wound bed).
- If extensive bleeding is observed after sharp debridement, the bleeding must be controlled before applying Dermagraft; no topical agents may be used to stop the bleeding.



## **MATERIALS REQUIRED FOR PREPARATION AND APPLICATION OF DERMAGRAFT®**

- Water bath/thawing tub (containing 37°C water) with lid
- Thermometer
- Sterilized scissors
- Surgical gloves
- Clock or timer
- Sterile normal saline (0.9% sodium chloride) at room temperature
- Permanent ink marker
- Sterilized blunt-end forceps
- Rinsing stand for Dermagraft
- Dressing supplies

## **PREPARATION FOR USE**

**CAUTION:** Do not use Dermagraft after the expiration date indicated on the labeled unit carton.

**CAUTION:** Follow all instructions to ensure delivery of metabolically active, living cells to the patient's wound.

**CAUTION:** Do not use the product if there is evidence of container damage or if the time on the shipping box has expired.

**CAUTION:** Product must remain frozen at  $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until ready to thaw. Do not reuse, refreeze, or sterilize this product or its container.

NOTE: The transfer of Dermagraft from freezer or original shipping container into the 34°C to 37°C water bath must take no longer than 60 seconds to ensure delivery of living cells to the patient's wound.

NOTE: Do not thaw more than one (1) piece of Dermagraft in the same water bath at the same time.

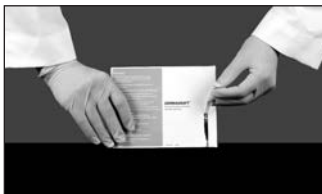
1. For each bag containing Dermagraft®, prepare a 2-liter water bath or thawing tub containing 2 liters of water at 34°C to 37°C. Water temperature must not exceed 37°C.



2. Remove the box containing Dermagraft from either the freezer or the shipping box per the Storage and Transfer Instructions found in the shipping box. Close the freezer door or the shipping box, and then immediately begin the thawing process, as detailed below.



3. Tear the cardboard box open along perforation.



4. Remove the foil pouch from the box.



5. Tear open the foil pouch with your hands at the tear notch.



NOTE: Do not cut foil pouch with scissors.

6. Remove the clear bag containing Dermagraft®. Do not open the clear bag.



NOTE: During the thawing and rinsing steps, touch the outer margins of the bag only and avoid touching the areas of the bag that come in contact with Dermagraft.

7. Within 60 seconds of removal from the freezer or original shipping container, completely submerge the clear bag in the 34°C to 37°C water. Place the thawing tub lid on the tub during the thawing process to keep the Dermagraft® submerged. Water temperature does not need to be monitored from this point. Allow approximately two (2) minutes for thawing. The process is complete when there are no visible ice crystals within the clear bag.

NOTE: Do not thaw longer than three (3) minutes to ensure delivery of living cells to the patient's wound.

NOTE: Due to capillary action, small amounts of growth medium can enter the pockets formed by the bottom welds. Cell growth medium contains the pH indicator phenol red, which becomes yellow in acidic conditions. The existence of pockets with colored fluid (i.e. red or yellow) has no impact on the safety or efficacy of Dermagraft.



8. Promptly remove the thawing tub lid and remove the clear bag from the water.

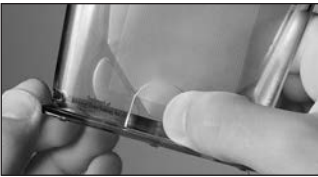


9. Handling by the clear bag's outer margins, place the bag into the rinsing stand without touching the areas of the bag that come in contact with Dermagraft®.



NOTE: A thin layer of cells in addition to the Dermagraft may be present inside the clear bag. This is a normal result of the manufacturing process.

10. Secure the clear bag inside the rinsing stand by using the locking clip at the bottom of the stand. Leave the bag in this locked position throughout the rinsing procedure. Immediately begin the rinsing process (Steps 11-15).

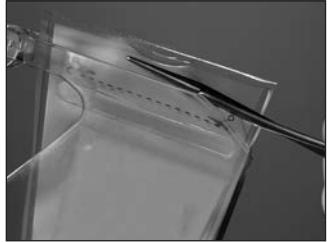


NOTE: Steps 11-15 should be carried out promptly and without interruption to ensure delivery of living cells to the patient's wound.

CAUTION:

**Dermagraft® is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided. Nitrile gloves work well to prevent contact with the DMSO cryoprotectant.**

11. Put on surgical gloves and cut the clear bag open above the cut line with sterilized scissors.



12. Gently squeeze the solid plastic bar to open the clear bag. Pour the liquid out. Gently fill the bag up to the plastic bar with room temperature sterile normal saline. Wait for five (5) seconds and then pour out the saline.



NOTE: If detached welds are present, then care must be taken to ensure the Dermagraft piece remains in the clear bag during rinsing. Pinching the top of the clear bag partially close while pouring the saline rinses out will ensure the piece is retained in the bag.

13. Refill the clear bag to the bar a second time with room temperature sterile normal saline. Wait for five (5) seconds and then pour out the saline.

- 14. Refill the clear bag to the bar again with room temperature sterile normal saline. Wait for five (5) seconds and then pour out the saline. The product has now been rinsed three (3) times.
  
- 15. Fill the clear bag a fourth time with sterile normal saline and hold. If you are immediately ready to implant the product, hold the product in the saline for a minimum of five (5) seconds and then proceed to Step 16. If the patient is not ready or you need to transport the product to the patient, then cap the rinsing stand. Dermagraft may be held in saline up to 30 minutes.



NOTE: Do not hold Dermagraft® at room temperature for more than 30 minutes to ensure delivery of living cells to the patient's wound. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation for Use instructions.

NOTE: Dispose of all liquid, rinsing solutions, and unused pieces of Dermagraft in accordance with institution or government environmental regulations.

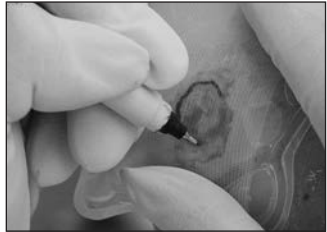
## APPLICATION

**CAUTION:** Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on an ulcer being treated with Dermagraft® as such preparations may cause reduced viability of Dermagraft.

16. When ready for application, completely drain the clear bag of liquid. Then release the locking clip and remove the bag from the rinsing stand.

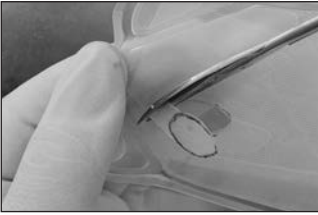


17. Holding the clear bag by the outer margins, use a permanent marker to trace the edge of the wound onto the bag either directly or from a separate tracing of the ulcer.

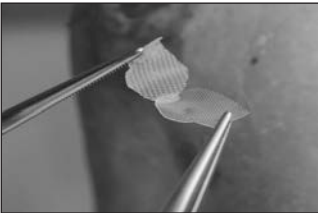




18. Using sterilized scissors, cut the Dermagraft® from the edge of the clear bag along the traced lines making allowance for the wound depth, and creating a handling tab to facilitate the implantation of Dermagraft.



19. Carefully peel the plastic from both sides of the Dermagraft using sterilized forceps.



20. Implant the Dermagraft into the debrided ulcer, covering the surface of the wound to just below the epithelial layer ensuring no air is trapped between Dermagraft and the wound surface. With sterilized scissors, trim the excess handling tab.



21. Cover the wound with a non-adherent dressing. Fill, but do not pack, the wound with a dressing that provides a moist wound environment.



22. Between routine applications of Dermagraft<sup>®</sup>, it is important to maintain a moist wound environment.
23. After the initial application of Dermagraft, subsequent sharp debridement of the wound should continue as necessary. Subsequent wound preparation should minimize disruption or removal of previously implanted Dermagraft.
24. Following each application of Dermagraft, the first wound dressing change should take place in approximately 72 hours.

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NOTE: If a dressing change is needed prior to 72 hours, the non-adherent dressing layer should be left in place.

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## **DERMAGRAFT® HUMAN FIBROBLAST-DERIVED DERMAL SUBSTITUTE ESSENTIAL PRESCRIBING INFORMATION**

Numbers in parentheses ( ) refer to sections in the main part of the product labeling.

### **DEVICE DESCRIPTION**

Dermagraft is a cryopreserved human fibroblast-derived dermal substitute. (1)

### **INTENDED USE/INDICATIONS**

Dermagraft is indicated for use in the treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure.

Dermagraft should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. (2)

### **CONTRAINDICATIONS**

- Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts.
- Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution. (3)

### **WARNINGS**

None (4)

## PRECAUTIONS

CAUTION: The product must remain frozen at  $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$  continuously until ready for use.

CAUTION: Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on an ulcer being treated with Dermagraft® as such preparations may cause reduced viability of Dermagraft.

CAUTION: Do not reuse, refreeze, or sterilize the product or its container.

CAUTION: Do not use the product if there is evidence of container damage or if the date and time stamped on the shipping box has expired.

CAUTION: Dermagraft is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided.

CAUTION: Dermagraft has not been studied in patients receiving greater than 8 device applications.

CAUTION: Dermagraft has not been studied in patients with wounds that extend into the tendon, muscle, joint capsule, or bone. Dermagraft has not been studied in children under the age of 18 years, in pregnant women, in patients with ulcers over a Charcot deformity of the mid-foot, or in patients receiving corticosteroids or immunosuppressive or cytotoxic agents.

CAUTION: To ensure the delivery of metabolically active, living cells to the patient's wound, do not hold Dermagraft at room temperature for more than 30 minutes. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation for Use instructions.

**CAUTION:** The persistence of Dermagraft® in the wound and the safety of this device in diabetic foot ulcer patients beyond six months has not been evaluated. Testing has not revealed a tumorigenic potential for cells contained in the device. However, the long-term response to these cells is unknown.

**CAUTION:** Always thaw and rinse product according to the Preparation for Use instructions to ensure the delivery of metabolically active, living cells to the patient's wound.

**CAUTION:** Do not use Dermagraft after the expiration date indicated on the labeled unit carton. (5)

## **ADVERSE EVENTS**

In clinical studies conducted to date, the overall incidence of reported adverse events was approximately the same for patients who received Dermagraft compared to those who received the Control treatment. (6)

## **MAINTAINING DEVICE EFFECTIVENESS**

Dermagraft must be stored continuously at  $-75^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . Dermagraft must be thawed and rinsed according to the Preparation for Use instructions. After the initial application of Dermagraft, subsequent sharp debridement of the ulcer should continue as necessary. Additional wound preparation should minimize disruption or removal of previously implanted Dermagraft. (13)

## **PATIENT COUNSELING INFORMATION**

After implantation of Dermagraft, patients should be instructed not to disturb the ulcer site for approximately 72 hours (three days). After this time period, the patient, or caregiver, should perform the first dressing change. The frequency of additional dressing changes should be determined by the treating physician. Patients should

be given detailed instructions on proper wound care so they can manage dressing changes between visits. Compliance with off weight-bearing instructions should be emphasized. Patients should be advised that they are expected to return for follow-up treatments on a routine basis, until the ulcer heals or until they are discharged from treatment. Patients should be instructed to contact their physician, if at any time they experience pain or discomfort at the ulcer site or if they notice redness, swelling, or discharge around/from the ulcer. (8)

## **HOW SUPPLIED**

Dermagraft® is supplied frozen in a clear bag containing one piece of approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application. The clear bag is enclosed in a foil pouch and labeled unit carton.

**CAUTION:** Dermagraft is limited to single-use application. Do not reuse, refreeze, or sterilize the product or its container.

Dermagraft is manufactured using sterile components and is grown under aseptic conditions. Prior to release for use, each lot of Dermagraft must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability.

Dermagraft is packaged with a saline-based cryoprotectant. This solution is supplemented with 10% DMSO (Dimethylsulfoxide) and bovine serum to facilitate long-term frozen storage of the product. Refer to the step-wise thawing and rinsing procedures to ensure delivery of a metabolically active product to the wound bed. (9)

**Customer Assistance:**

For product orders, technical support, product questions, reimbursement information, or to report any adverse reactions or complications, please call the following number which is operative 24 hours a day:

**Dermagraft Customer Service**

(877) DERMAGRAFT or (877) 337-6247

*CAUTION: Federal (U.S.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).*

**Organogenesis Inc.**

US PAT Nos.  
4,963,489; 5,266,480; 5,443,950

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**Organogenesis** inc.

LIVING TECHNOLOGY



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