Integra® Omnigraft™
Dermal Regeneration Matrix

DESCRIPTION

Integra® Omnigraft™ Dermal Regeneration Matrix (Omnigraft), available in Meshed and Non-Meshed configurations, is an advanced bilayer matrix for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of bovine collagen and chondtroitin-6-sulfate (C6S) that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Omnigraft, also marketed as Integra® Dermal Regeneration Template, is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Omnigraft should not be re-sterilized.

INDICATIONS

Integra® Omnigraft Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Integra® Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

CONTRAINDICATIONS

- Omnigraft should not be used in patients with known sensitivity to bovine collagen or chondroitin materials.
- Omnigraft should not be used on clinically diagnosed infected wounds.

WARNINGS

Debridement or excision must be done thoroughly to remove any remaining necrotic tissue that may delay healing or cause infection. Omnigraft will not incorporate into a wound bed of nonviable tissue. Leaving any remaining nonviable tissue may create an environment for bacterial growth.

PRECAUTIONS

- The following complications are possible with the use of wound treatments. The product should be removed if any of these conditions occur: infection, chronic inflammation (initial application of wound products may be associated with

transient, mild, localized inflammation), allergic reaction, excessive redness, pain, or swelling.

- Do not re-sterilize. Discard all opened and unused portions of Omnigraft.
- Omnigraft is sterile if the package is unopened and undamaged. Do not use if the package seal is broken.
- Discard Omnigraft if mishandling has caused possible damage or contamination.
- There have been no clinical studies evaluating Omnigraft in pregnant women. Caution should be exercised before using Omnigraft in pregnant women. Such use should occur only when the anticipated benefit clearly outweighs the risk.
- Do not use enzymatic debridement agents when cleaning out the wound.
- Omnigraft should be applied on the day of debridement. Delaying the application of Omnigraft may substantially impair the take of the material to the wound bed.
- Hemostasis must be achieved prior to applying Omnigraft. Inadequate control of bleeding will interfere with the incorporation of Omnigraft.
- Appropriate bolstering techniques should be used so Omnigraft maintains intimate contact with the wound bed.
- Keep the dressings dry and avoid contact with water at all times.
- Omnigraft must NOT be excised off the wound.
- Caution must be employed to not remove the newly formed dermal tissue when removing the silicone layer.
- Placing the patient in hydrotherapy immersion may interfere with proper incorporation of Omnigraft and cause premature separation of the silicone layer and non-adherence to the wound bed.
- Appropriate offloading techniques to minimize pressure and shearing should be used to reduce the risk of mechanical dislodgement.

ADVERSE EVENTS

a) Neuropathic Diabetic Foot Ulcer Clinical Trial

All adverse events at a frequency of ≥ 1% in either cohort that were observed in the clinical trial evaluating Omnigraft for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care are presented in Table 1. This table includes adverse events that were both attributed to and not attributed to treatment. The adverse events are listed in descending order according to their frequency in the Omnigraft cohort.

Table 1: Adverse Events Reported in Greater than 1% of Patients in the Neuropathic Diabetic Foot Ulcer Clinical Trial

Adverse Event	**Omnigraft N = 154 Patients n (n/N%)**	**Control N = 153 Patients n (n/N%)**
Diabetic foot infection	23 (14.9)	23 (15.0)
Diabetic foot*	22 (14.3)	31 (20.3)
Pain in extremity	14 (9.1)	20 (13.1)
Cellulitis	13 (8.4)	13 (8.5)
Osteomyelitis	9 (5.8)	19 (12.4)
Edema peripheral	7 (4.5)	7 (4.6)
Nausea	7 (4.5)	3 (2.0)
Condition aggravated	6 (3.9)	14 (9.2)
Excoriation	6 (3.9)	7 (4.6)
Upper respiratory tract infection	6 (3.9)	6 (3.9)
Blister	6 (3.9)	6 (3.9)
Influenza	5 (3.2)	3 (2.0)
Wound	4 (2.6)	6 (3.9)
Pneumonia	4 (2.6)	3 (2.0)
Vomiting	4 (2.6)	2 (1.3)
Hypoglycemia	4 (2.6)	1 (0.7)
Ingrown nail	4 (2.6)	1 (0.7)
Urinary tract infection	3 (1.9)	6 (3.9)
Erythema	3 (1.9)	4 (2.6)
Cardiac failure congestive	3 (1.9)	4 (2.6)
Pyrexia	3 (1.9)	3 (2.0)
Application site pain	3 (1.9)	2 (1.3)
Diarrhea	3 (1.9)	2 (1.3)
Hypertension	3 (1.9)	2 (1.3)
Disease recurrence	3 (1.9)	1 (0.7)
Local swelling	3 (1.9)	1 (0.7)
Skin maceration	3 (1.9)	1 (0.7)
Application site erosion	3 (1.9)	—
Contusion	3 (1.9)	—
Decubitus ulcer	2 (1.3)	4 (2.6)
Nasopharyngitis	2 (1.3)	2 (1.3)
Constipation	2 (1.3)	2 (1.3)
Gastro-esophageal reflux disease	2 (1.3)	2 (1.3)
Diabetic neuropathy	2 (1.3)	2 (1.3)
Dizziness	2 (1.3)	2 (1.3)
Asthma	2 (1.3)	2 (1.3)

Adverse Event	**Omnigraft N = 154 Patients n (n/N%)**	**Control N = 153 Patients n (n/N%)**
Cough	2 (1.3)	2 (1.3)
Dyspnea	2 (1.3)	2 (1.3)
Pain	2 (1.3)	2 (1.3)
Sinusitis	2 (1.3)	1 (0.7)
Chest pain	2 (1.3)	1 (0.7)
Hypotension	2 (1.3)	—
Renal failure	2 (1.3)	—
Blood glucose decreased	2 (1.3)	—
Blood pressure increased	2 (1.3)	—
Anxiety	2 (1.3)	—
Arthralgia	1 (0.6)	6 (3.9)
Laceration	1 (0.6)	5 (3.3)
Abscess limb	1 (0.6)	4 (2.6)
Gastritis	1 (0.6)	3 (2.0)
Balance disorder	1 (0.6)	3 (2.0)
Drug hypersensitivity	1 (0.6)	3 (2.0)
Nail avulsion	1 (0.6)	2 (1.3)
Sepsis	1 (0.6)	2 (1.3)
Gout	1 (0.6)	2 (1.3)
Muscle spasms	1 (0.6)	2 (1.3)
Musculoskeletal pain	1 (0.6)	2 (1.3)
Skin fissures	1 (0.6)	2 (1.3)
Headache	1 (0.6)	2 (1.3)
Coronary artery disease	1 (0.6)	2 (1.3)
Visual impairment	1 (0.6)	2 (1.3)
Anemia	1 (0.6)	2 (1.3)
Localized infection	—	4 (2.6)
Gangrene	—	3 (2.0)
Diabetes mellitus	—	3 (2.0)
Diabetic ketoacidosis	—	3 (2.0)
Limb injury	—	3 (2.0)
Cataract	—	3 (2.0)
Hyperlipidemia	—	2 (1.3)
Skin ulcer	—	2 (1.3)
Paronychia	—	2 (1.3)
Skin infection	—	2 (1.3)
Soft tissue infection	—	2 (1.3)
Hypoesthesia	—	2 (1.3)

Adverse Event	Omnigraft N = 154 Patients n (n/N%)	Control N = 153 Patients n (n/N%)
Pulmonary embolism	—	2 (1.3)
Skin papilloma	—	2 (1.3)

*Diabetic foot includes new, worsening, and recurring ulcers.

Serious Adverse Events (SAE): 38/154 (24.7%) of the Omnigraft and 55/153 (35.9%) of the Control subjects reported a SAE. The incidence of serious infections and infestations was 27/154 (17.5%) in the Omnigraft and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection (i.e., 8/154 (5.2%) of the Omnigraft and 15/153 (9.8%) of the Control subjects). Four Control and zero Omnigraft subjects died during the study.

Adverse Events potentially related to treatment (TRAE) occurred in 7/154 (4.5%) of the Omnigraft and 8/153 (5.2%) of the Control subjects. In the Omnigraft group, the TRAEs were: diabetic foot infections (3.2%; 5/154), application site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). In the Control group, the TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153).

b) U.S. Burn Clinical Trials

Omnigraft, evaluated under the marketed trade name of Integra® Dermal Regeneration Template (Integra template), has been found to be well tolerated in 4 prospective clinical trials involving 444 burn patients. There were no reports of clinically significant immunological or histological responses to the implantation of Integra template. There were no reports of rejection of Integra template.

Adverse events in the Postapproval study were similar to those observed in the previous clinical trials and are common in populations of critically ill burn patients regardless of type of treatment used. There were no trends noted. There were 6 adverse events which were rated by the investigator as being related. These events were all single occurrences except for sepsis (2). These adverse events occurred in less than 1% of the safety population.

Table 2: Adverse Events Reported in Greater than 1% of Patients in the Postapproval Study

Adverse Event	Postapproval Study N = 216 Patients n/N (%)
Sepsis	50/216 (23.1%)
Death	30/216 (13.9%)
Infection	6/216 (2.8%)
Thrombophlebitis	6/216 (2.8%)
Kidney Failure	6/216 (2.8%)
Necrosis	5/216 (2.3%)
Hemorrhage	5/216 (2.3%)
Heart Arrest	4/216 (1.9%)
Apnea	4/216 (1.9%)
Pneumonia	4/216 (1.9%)
Allergic Reaction	3/216 (1.4%)
Fever	3/216 (1.4%)
Multisystem Failure	3/216 (1.4%)
Atrial Fibrillation	3/216 (1.4%)
Gastrointestinal Hemorrhage	3/216 (1.4%)
Kidney Abnormal Function	3/216 (1.4%)

Adverse events reported in less than 1% of the population were as follows: enlarged abdomen, accidental injury, hypothermia, peritonitis, hypotension, peripheral vascular disorder, arrhythmia, cardiomyopathy, cardiovascular disorder, congestive heart failure, pulmonary embolism, dyspnea, aspiration pneumonia, hypoxia, pleural effusion, respiratory distress syndrome, cholecystitis, gastro intestinal perforation, hepatorenal syndrome, intestinal obstruction, and pancreatitis.

Table 3: Adverse Events Reported in Greater than 1% of Patients in Previous Studies

Adverse Event	Multi-center N = 149 Patients n/N (%)	Anatomic Site N = 59 Patients n/N (%)	Meshed vs. Sheet N = 20 Patients n/N (%)
Death	37/149 (24.8%)	19/59 (32.2%)	3/20 (15%)
Sepsis	17/149 (11.4%)	4/59 (6.8%)	1/20 (5.0%)
Apnea	13/149 (8.7%)	5/59 (8.5%)	0/20 (0.0%)
Pneumonia	10/149 (6.7%)	0/59 (0.0%)	0/20 (0.0%)
Heart Arrest	7/149 (4.7%)	6/59 (10.2%)	0/20 (0.0%)
Kidney Failure	5/149 (3.4%)	4/59 (6.8%)	0/20 (0.0%)
Respiratory Distress	3/149 (2.0%)	0/59 (0.0%)	0/20 (0.0%)

Adverse Event	**Multi-center N = 149 Patients n/N (%)**	**Anatomic Site N = 59 Patients n/N (%)**	**Meshed vs. Sheet N = 20 Patients n/N (%)**
Infection	2/149 (1.3%)	0/59 (0.0%)	0/20 (0.0%)
Lung Disease	2/149 (1.3%)	0/59 (0.0%)	0/20 (0.0%)
Dyspnea	1/149 (0.7%)	1/59 (1.7%)	0/20 (0.0%)
Adrenal Insufficiency	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Agitation	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Convulsion	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Hematemesis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Hemoptysis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Liver Cirrhosis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Nonadherence	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Shock	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Skin Discoloration	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Asystole	0/149 (0.0%)	0/59 (0.0%)	1/20 (5.0%)
Cerebral Artery Infarct	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Metastatic Ovarian Cancer	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Peritonitis	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Sarcoidosis	0/149 (0.0%)	0/59 (0.0%)	1/20 (5.0%)
Third Degree Burn	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Multisystem Failure	0/149 (0.0%)	3/59 (5.1%)	0/20 (0.0%)

The adverse events directly related to the use of Integra template were: wound fluid accumulation, positive wound cultures, and clinical wound infection.

In these clinical trials, data were collected regarding wound infection. The consequences of infection at sites treated with Integra template included partial or complete loss of take (incorporation into the wound bed) of Integra template. Infection rates in sites treated with Integra template in the three clinical trials supporting the PMA ranged from 14 to 55%. The overall infection rate for the Postapproval Study was 16.3%.

c) Scar Contracture Reconstruction Study

The following adverse events were reported in a Reconstructive Surgery Study involving 20 patients with 30 anatomical sites and a Retrospective Contracture Reconstruction Survey involving 89 patients and 127 anatomic sites.

Table 4: Adverse Events Reported in Greater than 1% of Patients in the Reconstructive Contracture Surgery Study and Retrospective Contracture Reconstruction Survey

Adverse Event	Reconstructive Surgery Study N = 30 Sites n/N (%)	Retrospective Contracture Reconstruction Survey N = 127 Sites n/N (%)
Infection	0/30 (0.0%)	26/127 (20.5%)
Fluid under Silicone Layer	0/30 (0.0%)	18/127 (14.2%)
Partial graft loss (Integra)	0/30 (0.0%)	2/127 (1.6%)
Failure to take (Integra)	0/30 (0.0%)	8/127 (6.3%)
Shearing/Mechanical shift (loss of Integra)	1/30 (3.3%)	6/127 (4.7%)
Hematoma	5/30 (16.7%)	3/127 (2.3%)
Granulation tissue formation	0/30 (0.0%)	4/127 (3.1%)
Delayed Healing	0/30 (0.0%)	1/127 (0.8%)
Separation of the Silicone Layer	0/30 (0.0%)	1/127 (0.8%)
Seroma	0/30 (0.0%)	1/127 (0.8%)
Pruritis	0/30 (0.0%)	1/127 (0.8%)
Epidermal autograft loss >15%	2/30 (6.7%)	7/127 (5.5%)
Epidermal autograft loss <15%	7/30 (23.3%)	9/127 (7.1%)

There were no infections reported in the Reconstructive Surgery Study and the reported infection rate was 20.5% in the Retrospective Contracture Reconstruction Survey. No deaths were reported.

d) Postmarket Surveillance

Table 5 lists the 111 clinical Medical Device Reports (MDRs) that occurred since 1996 with Integra.

Table 5: Summary of Clinical MDRs of Integra® Product Family Since 1996

MDR Category	Total MDRs
Infection	60
Poor Take/Dislodgment	18
Allergic Reaction	6
Autograft Lost	4

Wound Dehiscence	4
Regeneration of Granulous Skin	3
Death*	3
No Autograft Take	3
Non healing Wound	2
Matrix Calcification	2
Septic Shock	1
Hematoma	1
Fever	1
Hypertrophic Scarring	1
Bulging of Graft	1
Factor 5 Deficiency**	1
Total	**111**

* The three deaths that Integra filed as MDRs were deemed by the physicians who reported the complaints to be unrelated to the Integra template.

** Integra investigators determined that Factor 5 Deficiency could not have been caused by the Integra product. The complaint was filed because a physician thought that the product could have caused the deficiency based on his research that bovine thrombin has been known to cause the deficiency. Integra products do not contain bovine thrombin and could not have caused the Factor 5 Deficiency.

SUMMARY OF CLINICAL STUDIES

a) Neuropathic Diabetic Foot Ulcer Clinical Trial

Clinical Trial IDRT/DFU US 2009-3 was a prospective, multi-center (32 sites), open-label, randomized (stratification by ulcer size) concurrently controlled pivotal study in subjects with partial or full thickness diabetic foot ulcers located distal to the malleolus with controlled diabetes and without significant compromise of arterial circulation. Subjects who met the entry criteria were enrolled in a two-week Pre-Treatment Phase while they received standard of care treatment for their study ulcer. Subjects who continued to meet the entry criteria after the Pre-Treatment Phase (e.g., an ulcer whose size decreased less than 30%) were randomized to a 16 week Treatment Phase with either: Omnigraft + Standard of Care (Treatment) or Standard of Care alone (Control). At the conclusion of the Treatment Phase subjects underwent three additional monthly visits in the Follow-up Phase to monitor open or healed ulcer status.

The primary effectiveness endpoint was the percentage of subjects with complete study ulcer closure as assessed by the Investigator, during the 16 week Treatment Phase.

The primary safety endpoint was the incidence of adverse events recorded during the study (i.e., the Pre-Treatment, Treatment and Follow-up Phases). Safety evaluations also included assessment of serum chemistry values at Pre-Treatment Phase and the end of Treatment Phase visits.

Study Population Demographics and Baseline Parameters

The baseline demographics in the Omnigraft and Control arms were comparable for all parameters evaluated (Table 6).

Table 6: ITT Baseline Population Demographics and Baseline Characteristics

Characteristic	**Statistic**	**Omnigraft (N = 154)**	**Control (N = 153)**	**Total (N = 307)**
Age (years)	Mean (SD)	55.8 (10.6)	57.3 (9.7)	56.5 (10.1)
	Median	56.0	57.0	57.0
	Min, Max	31.0, 82.0	28.0, 82.0	28.0, 82.0
Gender	Male, n (n/N%)	118 (76.6)	114 (74.5)	232 (75.6)
	Female, n (n/N%)	36 (23.4)	39 (25.5)	75 (24.4)
Race	American Indian/Alaskan Native, n (n/N%)	0 (0.0)	2 (1.3)	2 (0.6)
	Asian, n (n/N%)	1 (0.6)	2 (1.3)	3 (1.0)
	Black Or African American, n (n/N%)	28 (18.2)	34 (22.1)	62 (20.1)
	Native Hawaiian or Pacific Islander, n (n/N%)	1 (0.6)	0 (0.0)	1 (0.3)
	Caucasian, n (n/N%)	118 (76.6)	111 (72.1)	229 (74.4)
	Other, n (n/N%)	6 (3.9)	5 (3.2)	11 (3.6)
Ethnicity	Not Hispanic/Latino, n (n/N%)	108 (70.1)	116 (75.8)	224 (73.0)
	Hispanic or Latino, n (n/N%)	46 (29.9)	37 (24.2)	83 (27.0)
Weight (kg)	Mean (SD)	107 (23.3)	107 (28.9)	107 (26.2)
	Median	105	103	104
	Min, Max	63.5, 178	52.2, 221	52.2, 221
Height (cm)	Mean (SD)	178 (9.4)	177 (12.2)	177 (10.9)
	Median	178	180	178
	Min, Max	154, 196	132, 203	132, 203
BMI (kg/m²)	Mean (SD)	34.0 (7.2)	34.1 (8.4)	34.0 (7.8)
	Median	33.8	32.1	33.0
	Min, Max	21.4, 58.9	19.9, 62.4	19.9, 62.4
Tobacco	Yes, n (n/N%)	28 (18.2)	19 (12.4)	47 (15.3)

Product Use	No, n (n/N%)	126 (81.8)	134 (87.6)	260 (84.7)
Diabetes Mellitus Type	Type 1, n (n/N%)	4 (2.6)	13 (8.5)	17 (5.5)
	Type 2, n (n/N%)	150 (97.4)	140 (91.5))	290 (94.5
Use Of Insulin at Baseline	Yes, n (n/N%)	30 (19.5)	37 (24.2)	67 (21.8)
	No, n (n/N%)	124 (80.5)	116 (75.8)	240 (78.2)
Age Of Study Ulcer (Days)	N	154	153	307
	Mean (SD)	308 (491)	303 (418)	305 (455)
	Median	126	152	140
	Min, Max	31.0, 4501	32.0, 2059	31.0, 4501
% Reduction in Ulcer Area Size Between Screening & First Treatment Application	Mean (SD)	-14 (38.0)	-17 (65.9)	-16 (53.7)
	Median	-3.4	-1.6	-2.0
	Min, Max	-228, 29.2	-565, 28.6	-565, 29.2
Baseline Study Ulcer Size (cm^2)	Mean (SD)	3.53 (2.5)	3.65 (2.6)	3.59 (2.6)
	Median	2.6	2.6	2.6
	Min, Max	1.0, 11.5	1.0, 10.8	1.0, 11.5
Location of Study Ulcer	Plantar, n (n/N %)	126 (81.8)	127 (83.0)	253 (82.4)
	Dorsal, n (n/N %)	28 (18.1)	25 (16.3)	53 (17.3)
	Medial, n (n/N %)	0	1 (0.7)	1 (0.3)
Wagner Grade	Grade 1, n (n/N %)	45 (29.2)	37 (24.2)	82 (26.7)
	Grade 2, n (n/N %)	109 (70.8)	116 (75.8)	225 (73.3)

Results

545 subjects were screened and 307 patients were randomized to treatment (i.e., 154 Omnigraft and 153 Control subjects).

Effectiveness

The primary effectiveness endpoint was complete study ulcer closure during the 16-week Treatment Phase, as assessed by the Investigator. 79/154 (51.3%) of the Omnigraft and 49/153 (32.0%) of the Control subjects achieved 100% complete closure of the study ulcer ($p = 0.0007$).

Clinically significant improvements in patient outcome were also observed in the following secondary effectiveness endpoints: 1) complete wound closure via computerized planimetry, 2) time to complete wound closure (by both Investigator and

computerized planimetry assessments), and 3) the rate of wound size reduction per week. Similar to the primary endpoint, when assessed by computerized planimetry, 77/154 (50.0%) of the Omnigraft and 48/153 (31.4%) of the Control subjects achieved 100% complete closure of the study ulcer (p=0.0010). For subjects that healed, the median time to wound closure was 43 and 78 days for the Omnigraft and Control cohorts, respectively (by both Investigator and computerized planimetry assessments). At the final treatment visit, the average rate of wound closure (by the planimetry assessments) was 7.15% and 4.81% for the Omnigraft and Control cohorts, respectively (p=0.0115)

Omnigraft subjects showed improvement in the Physical Functioning for Daily Activities and Reduction in the Bodily Pain modules of the Quality of Life Questionnaire SF-36v2 Health Survey questionnaire. No significant differences between treatment groups were observed for General Health, Social Functioning, Role Emotional, Mental Health or Vitality Modules of this questionnaire.

15/79 (19.0%) of the Omnigraft and 13/49 (26.5%) of Control subjects experienced ulcer recurrence during the study. The difference was not statistically significant.

Additional Analyses

Number of Omnigraft Applications – Table 7 provides a summary of the number of subjects and the number of Omnigraft applications required. Reapplications were at the discretion of the investigator.

Table 7: Summary of Omnigraft Applications

No. of Applications	**No. Omnigraft Subjects N = 154 n (n/N %)**
1	92 (59.7)
2	33 (21.4)
3	12 (7.8)
4	5 (3.2)
5	5 (3.2)
6	2 (1.3)
7	2 (1.3)
11	2 (1.3)
15	1 (0.6)

Covariate Analyses – Baseline wound size and study ulcer age were significant factors for ulcer healing. Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, age, ethnicity, Wagner Grade, ulcer location (plantar/dorsal/medial), insulin use, or gender were not significant factors for wound healing.

At the conclusion of the Pre-Treatment and Treatment Phases of the trial, 128/154 (83.1%) of the Omnigraft and 117/153 (76.5%) of the Control subjects remained on study. 106/154 (68.8%) Omnigraft and 82/153 (53.6%) Control subjects completed the trial through follow-up. Based on the computerized planimetry assessment prior to

subject withdrawal during the treatment phase, a majority of withdrawals were due to the lack of treatment effectiveness in both groups, and the observed higher percentage of withdrawal in the control group appeared to be a reflection of the inferior performance of the Control treatment as compared to the Omingraft treatment. Also, no significant association between the treatment groups and subject discontinuation was observed for: 1) subjects with a history of lower extremity amputation and discontinuation during the Treatment Phase, 2) subjects with a history of cellulitis and discontinuation during the Treatment Phase, 3) subjects without a history of lower extremity infection and discontinuation during the Treatment Phase, 4) subjects with an additional ulcer at study entry and discontinuation during the Treatment Phase, 5) subjects with a prior history of foot surgery and discontinuation during the Treatment Phase, 6) the time that a subject remained on study prior to withdrawal, 7) the number of subjects who withdrew from the study during the Treatment Phase and experienced at least one major protocol deviation, 8) the amount of daily offloading or 9) the frequency of AEs and SAEs in both treatment cohorts. Therefore, the loss of these subjects did not significantly alter the evaluation of device safety and effectiveness.

b) Burn Studies

Integra template has been evaluated in over 1,200 wound sites in 444 burn patients in a series of 4 studies:

· Multi-center Safety and Efficacy Clinical Trial (Pivotal)
· Anatomic Site Study
· Meshed vs. Sheet Integra template Study
· Postapproval Study

Demographic, safety and effectiveness data for Integra template are summarized in the table below.

Table 8: Summary of Burn Clinical Trial Results

Variable		**Multi-center Study**	**Anatomical Site Study**	**Meshed vs. Sheet Study**	**Postapproval Study**
Year		**1983-1989**	**1985-1992**	**1989-1992**	**1997-2000**
Number of Patients	N	149	59	20	216
Number of Wound Sites		207	130	59	841
Age (years)	Mean ± SD	32.0 ± 21.5	49.2 ± 21.2	30.1 ± 15.6	34.7 ± 23.9
	Range	<1 – 88	19 – 93	4 – 59	<1 – 87

Variable		**Multi-center Study**	**Anatomical Site Study**	**Meshed vs. Sheet Study**	**Postapproval Study**

Gender	Male, n (n/N%)	112 (75.2%)	33 (55.9%)	16 (80%)	151 (69.9%)
	Female, n (n/N%)	37 (24.8%)	26 (44.1%)	4 (20%)	65 (30.1%)
Race	Caucasian, n (n/N%)	98 (65.8%)	56 (94.9%)	14 (70.0%)	151 (69.9%)
	Black, n (n/N%)	32 (21.5%)	0 (0.0%)	6 (30.0%)	38 (17.6%)
	Hispanic, n (n/N%)	15 (10.1%)	3 (5.1%)	0 (0.0%)	20 (9.2%)
	American Indian, n (n/N%)	3 (2.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Asian, n (n/N%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	4 (1.8%)
	Other, n (n/N%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
% BSA Total Burn	Mean ± SD	45.7 ± 18.6	49.8 ± 24.6	53.6 ± 19.4	36.5 ± 24.7
	Range	14.5 - 88.5	1 - 97	30 - 90	<1 - 95
% BSA Full-Thickness	Mean ± SD	31.8 ± 20.8	42.5 ± 24.0	35.4 ± 22.4	27.9 ± 24.4
	Range	0 - 88.5	1 - 95	0 - 78	0 - 95
% Inhalation Injury	%	42%	62.50%	50%	45%
Take	Mean	65.1%*	77.60%	80.60%	76.20%
	Median	80%*	95%	100%	98%
Infection	%	55%	14%	25%	16.30%
Mortality	%	24.80%	32%	15%	13.90%

*Paired comparative wound sites

Multi-center Safety and Efficacy Clinical Trial (Burn Pivotal Study)
In the pivotal multi-center clinical trial, 149 patients (with 207 total wound sites) were evaluated for safety and 106 patients (with 136 comparative wound sites) were included in an assessment of efficacy. The demographic profile was: mean age 32.0, age range <1 to 88 years, gender: 112 males and 37 females and a mean %TBSA burn of 45.7% with a range of 14.5%-88.5%. Take, which was defined as the median fractional area of the wound site to support epidermal growth, was the main efficacy variable and was bimodally distributed. In the multi-center trial, Integra template had successful take (take >10%) in 69% of the wound sites (94 of 136). For this group of wound sites with successful take, the mean take was 81%, and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 60% take. Integra template failed to take (take ≤10%) in 31% of the wound sites (42 of 136 comparative wound sites). For this group, the mean take was 1.7% and the median take was 0%.

The Integra template neodermis provided a viable surface for the successful transplantation of thin, meshed and spread epidermal autograft. The take of epidermal autograft was bimodally distributed. In the multi-center trial, epidermal autograft had successful take (take >10%) in 90.5% of the sites (95 of 105 comparative wound sites). For this group of wound sites with successful take, the mean was 84% and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 65% take. Epidermal autograft failed to take (take ≤10%) in 9.5% of the sites (10 of 105 comparative wound sites). For this group, the mean take was 1.7% take and the median take was 0%.

No significant difference was seen between the total time for burn healing for wounds treated with Integra template and for wounds treated with temporary wound covers. The healing time of thin epidermal autograft on the Integra template neodermis was comparable to that of conventional autograft. Donor sites for thin epidermal autograft healed faster and allowed for more cycles of reharvesting than conventional donor sites.

Histological Evaluation
Three hundred thirty-six serial biopsies were obtained from 131 patients participating in the multi-center clinical trial ranging from 7 days to 2 years after application of Integra template. A histological study of the wound healing in the burned areas was conducted. An intact dermis was achieved with regrowth of apparently normal reticular and papillary dermis. No scar formation appeared in the biopsies of patients examined.

Anatomic Site Study
In the noncomparative single-center anatomic site study, 59 patients (130 wound sites) were evaluated for safety and 41 patients (104 wound sites) were evaluated for efficacy parameters. The demographic profile was: mean age, 49.2, age range 19-93 years, gender: 33 males and 26 females and a mean %TBSA burn of 49.8% with a range of 1%-97%. The mean take of Integra template was 77.6%, and the median take was 95%. The mean take of the epidermal autograft was 77.8% and the median take was 85%. Median take was similar for the various anatomic locations evaluated. However, the small number of patients and noncomparative nature of the study prevented conclusions from being made.

Meshed vs. Sheet Study
A pilot study was conducted on 20 patients (59 wound sites) to compare 2:1 meshed (but not expanded) and sheet Integra template. The demographic profile was: mean age, 30.1, age range 4-59 years, gender: 16 males and 4 females and a mean % TBSA Burn of 53.6% with a range of 30-90%. The mean take of Integra template in this study was 80.6% and the median take was 100%, while the mean take for the epidermal autograft was 86.5% and the median take was 95%. However, due to the small number of patients and study design, statistical conclusions could not be drawn.

Postapproval Study

A Postapproval Study of Integra template evaluated the safety and effectiveness in 216 patients, 841 wound sites. There were 222 patients enrolled in the study, however 6 patients did not meet entry criteria (3 did not sign the patient informed consent form, 3 did not receive Integra template) resulting in 216 patients entered into the study. The demographic profile was: mean age 34.7, age range 4 months to 87 years, gender: 151 males and 65 females and a mean %TBSA burn of 36.5% with a range of <1% to 95%. Effectiveness was measured by graft take. Overall mean percent take for Integra template was 76.2% and the median percent take for Integra template was 98%. The mean take of epidermal autograft was 87.4% with median take of 95%. The rate of infection in the study patients was 16.3% (13.2% superficial and 3.1% invasive). Patient mortality was 13.9%. Data analysis indicated that mortality was related to patient age, percent total body surface area burned, presence of inhalation injury, and presence of infection at a non-Integra template treated wound site. Invasive infection at an Integra template wound site was not a significant risk factor for mortality.

c) Scar Contracture Reconstruction Studies

Reconstructive Surgery Study
This study evaluated the clinical and histologic outcomes in 20 consecutive patients (30 anatomic sites) whose scars and contractures were treated with Integra template. Patients' mean age was 27.6 years, with an age range of 4-54 years. Patient follow-up ranged from 3 to 24 months. The mean take was derived from the adverse event data and was calculated to be 94.2% for Integra template and 86.3% for epidermal autograft. Efficacy was evaluated using the Vancouver Burn Scar Assessment scale by an independent review panel, a visual analog scale of patient satisfaction and histological evaluations of patient biopsies. The Vancouver Burn Scar Assessment scale ranges from 0 (normal) to 15. The mean preoperative Vancouver Burn Scar Assessment was 13.3 and the mean postoperative score was 9.0. For the patient satisfaction assessments, patients or their parents completed a questionnaire at least 3 months after the second stage of the reconstruction. A visual analog scale was used in which a score of 0%=preoperative scar and a score of 100%=normal skin with no scar. Patients/parents reported mean scores of 72% for range of movement, 62% for softness, 59% for appearance, 27% for pruritis and 14% for dryness.

Retrospective Contracture Reconstruction Survey
This survey requested information from physicians already using Integra template on the use of the product for contracture reconstruction. Information was received from 13 of 19 physicians surveyed who reported on 89 patients and 127 anatomic sites. The demographic profile for the reported patients was: mean age 24.8, age range <1 to 72, gender 52 males and 37 females. The safety results of this survey are provided in tabular form in the adverse event section.

INFORMATION FOR USE

Omnigraft is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

INSTRUCTIONS FOR USE

Sharp Debridement

1. Using aseptic technique, prepare the wound bed using standard methods to ensure the wound is free of debris and necrotic tissue.
2. Sharp debridement must be made to the level of viable tissue. Meticulous hemostasis needs to be achieved to prevent hematomas or excessive fluid accumulation. Omnigraft should not be applied over infected or deteriorating wounds until the underlying issue has been resolved.

Cleansing

1. Cleanse the wound thoroughly using a neutral, non-irritating, and non-toxic solution such as sterile saline or sterile water.

Product Preparation

1. To minimize the risk of infection, change your gloves following debridement and cleansing and before handling Omnigraft. A fresh set of sterile instruments are required for Omnigraft placement, shaping, and cutting.
2. Using aseptic technique, open the outer pouch and remove the inner foil pouch. Place the foil pouch flat on a sterile surface to open it. While holding the tab, remove the product from the pouch and peel off the protective plastic sheets.
3. Rinse the product with a sterile saline solution for at least 2 minutes. Carefully remove the tab from the product. Keep product in the basin until application.

NOTE: Before the application, Omnigraft can be pie crusted or fenestrated but must not be expanded. Fenestrations may improve the ability of the matrix to conform to irregular surfaces and may improve contact with the wound bed. DO NOT fenestrate pre-meshed product.

Product Application

1. Trim Omnigraft to size and apply immediately following wound bed preparation. The product should overlap the edges of the wound by 2mm. Any air bubbles should be carefully removed by moving them to the edge of the sheet using a gentle rolling motion to achieve intimate contact with the wound bed.

NOTE: It is critical that the collagen layer be in direct contact with the prepared wound bed. The silicone layer, identified by the black threads, must be placed away from the wound bed. Do not apply upside down; the black threads must be clearly visible. The black threads do not have to be placed in a certain orientation.

2. Omnigraft should be firmly secured using surgical staples or sutures so the product maintains intimate contact with the wound bed.
3. Appropriate bolstering may be used so Omnigraft maintains intimate contact with the wound bed.

4. After bolstering, use appropriate dressings to maintain product adherence and protect the wound area. The optimum secondary dressing is determined by wound location, size, depth, and user preference.

Post Application Care

1. Clinicians should change the dressings weekly without disturbing Omnigraft. Frequency of dressing changes will be dependent upon the volume of exudate produced, the type of dressing used, and the clinician's need to inspect the wound bed for signs of infection or healing.

   NOTE: Ensure that Omnigraft maintains intimate contact with the wound bed at all times. Be careful not to disturb Omnigraft.

   NOTE: Use a 15 blade scalpel to make an incision if hematoma or excess exudate exists.

2. Use an offloading device for patients following the application of Omnigraft to reduce shearing forces and to protect the wound site from future re-injury, especially on the plantar aspect of the foot.

Removal of Silicone Layer

1. If the edges of the silicone layer have separated from the wound site, the separated silicone can be trimmed.

   NOTE: The silicone layer of Omnigraft may be removed when the collagen layer has been replaced by neodermis, usually 14 to 21 days after application.

2. The clinician must be careful when removing the silicone layer. The silicone layer can usually be removed using only forceps. Generally, it should peel off easily. Difficulties in removal may indicate that the neodermis formation is incomplete.

   Caution: Do not remove the newly formed neodermal tissue when removing the silicone layer. Omnigraft must not be excised off the wound.

   Caution: If bleeding occurs, or if patient complains of excessive pain, stop and wait 1 to 2 additional days. Forced removal may result in wound re-injury.

   NOTE: It is recommended to always offload the ulcer until the wound has closed. To minimize recurrence, continue to offload to prevent future re-injury per the treating clinician's protocol.

POTENTIAL POST APPLICATION PROBLEMS

Wound Infection

Wounds having excessive discharge may require more frequent dressing changes and may require the use of appropriate antimicrobial intervention. The dressings should be

removed and wound sites inspected for infection. Appropriate diagnostic and therapeutic procedures should be followed.

Hematoma
Areas of hematoma should be monitored and aspirated or excised as required. New Omnigraft may be applied to the excised sites.

Poor Incorporation of Omnigraft
If Omnigraft is not incorporated into the wound bed, carefully remove the product and examine the wound bed. Areas of poor Omnigraft incorporation may be treated by reapplication of the product.

Premature Silicone Layer Separation
If the silicone layer separates from the wound bed after new dermal formation begins, only the loose area of the silicone layer needs to be removed.

PATIENT COUNSELING INFORMATION
Patients receiving Omnigraft should be counseled that: Omnigraft is to be used in combination with good ulcer care including an offloading device, optimal metabolic control, and proper nutrition. Once the ulcer has healed, ulcer prevention practices should be implemented including regular visits to the appropriate treating clinician. Patients should be given the patient brochure to remind them of this information.

TREATMENT OF DIABETES
Omnigraft does not address the underlying pathophysiology of diabetic foot ulcers. The patient's diabetes should be managed according to standard medical practice.

SINGLE USE DEVICE
Omnigraft is supplied in a single-use package and is guaranteed to be sterile and non-pyrogenic unless opened or damaged. The product is intended for use as an absorbable implant and is not to be reused. Any attempt to re-sterilize or reuse the product/components will damage the matrix and impair its ability to function as intended. All unused pieces must be discarded.

HOW SUPPLIED
Omnigraft is available in the following sizes:

Integra Omnigraft		
Product Codes	**Size**	**Quantity**
DFU4041	4 cm x 4 cm	1 unit/box
DFU7071	7 cm x 7 cm	1 unit/box
Integra Omnigraft Meshed		
Product Codes	**Size**	**Quantity**

MDFU4041	4 cm x 4 cm	1 unit/box
MDFU7071	7 cm x 7 cm	1 unit/box

The bilayer sheets consist of collagen with an outer removable silicone layer, which is identified by black suture markers to ensure proper placement of the sheets on the wound bed.

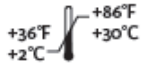
STORAGE
Store flat at room temperature: +2°C (+36°F) to +30°C (+86°F).

DISPOSAL
Product to be disposed according to institutional procedures.

PRODUCT INFORMATION DISCLOSURE
INTEGRA LIFESCIENCES CORPORATION HAS EXERCISED REASONABLE CARE IN THE SELECTION OF MATERIALS AND THE MANUFACTURE OF THESE PRODUCTS. INTEGRA LIFESCIENCES EXCLUDES ALL WARRANTIES, WHETHER EXPRESSED OR IMPLIED, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. INTEGRA LIFESCIENCES SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR CONSEQUENTIAL LOSS, DAMAGE, OR EXPENSE, DIRECTLY OR INDIRECTLY ARISING FROM USE OF THIS PRODUCT. INTEGRA LIFESCIENCES NEITHER ASSUMES NOR AUTHORIZES ANY PERSON TO ASSUME FOR IT ANY OTHER OR ADDITIONAL LIABILITY OR RESPONSIBILITY IN CONNECTION WITH THESE PRODUCTS.

SYMBOLS USED ON LABELING

	Do not re-use
	This product is not manufactured with Dry Natural Rubber or Natural Rubber Latex
	Do not re-sterilize
	Do not use if package is damaged
	Expiration date YYYY-MM-DD
	Sterilized using irradiation

LOT	Lot number
	Consult Instructions For Use
	Temperature limitation
	Manufacturer
REF	Catalog number
Rx ONLY	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or practitioner

Caution: Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or practitioner.

Please refer to the clinical training materials for complete instructions for use.
For product ordering information, technical questions, or reimbursement issues please call 877-444-1122 or 609-275-0500.

FDA APPROVED

Manufacturer:

Integra LifeSciences Corporation
311 Enterprise Drive, Plainsboro, NJ 08536
877-444-1122 USA
866-800-7742 fax
integralife.com

Made in the U.S.A.

U.S. Patent 6,969,523

RMS No: 7400010100 01/2015