Clinical Evidence for Diabetic Foot Ulcers
Based on Integra’s Bilayer Dermal Regeneration Matrix Technology, Integra developed Omnigraft® Dermal Regeneration Matrix specifically to help regenerate tissue and treat hard-to-heal DFUs in the outpatient wound care setting.

**Integra® Bilayer Wound Matrix** is indicated and used in the inpatient setting for the management of a wide range of wounds.

**Omnigraft®** is the Only FDA-Approved Product for use in the outpatient setting Indicated for Dermal Regeneration in the Treatment of DFUs.

Technologically advanced bilayer matrix designed to mimic skin by providing protection and dermal regeneration

**Silicone Layer Protects the Wound**
- Provides immediate coverage acting as temporary epidermal layer
- Maintains a moist wound environment
- Typically removed between 14 and 21 days

**Collagen/Chondroitin-6-Sulfate Matrix Promotes Dermal Regeneration**
- Acts as a dermal replacement layer
- Bioengineered acellular matrix minimizes inflammatory or immunogenic response
- 3D pore structure optimized for cellular and vascular ingrowth
Summary of Selected Published Clinical Data on Omnigraft and Bilayer Wound Matrix Dressing

Diabetic Foot Ulcers
Performed in Outpatient Setting


- Largest multicenter, prospective, randomized controlled trial (RCT) to date, evaluating CTPs in DFUs (32 Sites, 307 Subjects)
- Of those patients that healed:
  - 92% healed with two applications or less
  - 72% healed in just one application
- 5 week faster median time to complete wound closure when using Omnigraft vs standard of care
- 125% higher incidence of complete wound closure at 12 weeks using Omnigraft vs standard of care
- During the 14 day run-in period, only patients having DFUs that healed less than 30% were randomized into the clinical trial. This ensured the evaluated DFUs were chronic and the most difficult to heal

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment Group (n=154)</th>
<th>Control Treatment Group (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size at end of run-in: (cm², mean ± SD)</td>
<td>3.53 ± 2.5</td>
<td>3.65 ± 2.7</td>
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<tr>
<td>Ulcer age at enrollment: Days (± SD)</td>
<td>308 ± 491</td>
<td>303 ± 418</td>
</tr>
<tr>
<td>Wagner Grade 2 (%)</td>
<td>109 (70.8)</td>
<td>116 (75.8)</td>
</tr>
<tr>
<td>Location: Dorsal (%)</td>
<td>28.8 (18.2)</td>
<td>25 (16.5)</td>
</tr>
<tr>
<td>Plantar (%)</td>
<td>126 (81.8)</td>
<td>137 (83.6)</td>
</tr>
<tr>
<td>HbA1C (% mean ± SD)</td>
<td>8.0 ± 1.8 (64 mmol/mol)</td>
<td>8.2 ± 1.9 (64 mmol/mol)</td>
</tr>
</tbody>
</table>

Diabetic Foot Ulcers
Performed in OR Setting using Integra’s bilayer dermal regeneration matrix technology


- 30 patients underwent dermal regeneration template grafting over surgically debrided wound bed
- Complete wound healing occurred in 26 patients (86.7%)
- Average healing time was 74.1 days


- Case series where 5 patients with diabetes and deep foot wounds were grafted with Integra
- Average size of Integra grafted was 72.8 cm² and there was complete take of the Integra in all patients
- A well-vascularized neodermis developed in all patients


- A retrospective study of 105 patients reporting 83% limb salvage rate of diabetic patients with low risk of amputation
- Diabetic population had an average wound size of 25.9 cm²
- Average number of 1.28 operations before complete wound closure was achieved

* These clinical papers contain information regarding the use of Integra Dermal Regeneration Template to treat wounds for which Omnigraft is not indicated.
For more than 20 years, the Integra Dermal Regeneration Matrix Technology has demonstrated clinical success and has been evaluated in multiple clinical trials treating patients with 3rd-degree burns, scar reconstruction, and acute and chronic wounds in the operating room.

- **1988**: Artificial Dermis for Major Burns Multicenter RCT\(^1\) (149 Patients)
  - IDRT PMA Approved for Use in 3rd-Degree Burns

- **2001**: Use of Dermal Template in Contracture Release Procedures: A Multicenter Evaluation\(^2\) (89 Patients)
  - IDRT PMA Approved for Use in Scar Contracture

- **2003**: Multicenter Postapproval Clinical Trial of IDRT for Burn Treatment\(^3\) (216 Patients)

- **2004**: Reconstructive Surgery Using Artificial Dermis\(^4\) (31 Patients)

- **2014**: A Clinical Trial of Integra Template for Diabetic Foot Ulcer Treatment\(^5\) (307 Patients)
  - Omnigraft PMA Approved for DFUs

Now this powerful, proven solution is available for use in the outpatient setting.
Integra® Dermal Regeneration Template Brief Summary

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

Description: Integra Dermal Regeneration Template (Integra template) is a bilayer membrane system for skin replacement. The dermal replacement layer is made of a porous matrix of fibers of cross-linked bovine tendon collagen and glycosaminoglycan (chondroitin-6-sulfate) that is manufactured with a controlled porosity and defined degradation rate. The epidermal substitute layer is made of a thin polysiloxane (silicone) layer to control moisture loss from the wound. Integra template is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Integra template should not be re-sterilized.

Indications: Integra 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. Integra template is also indicated for the 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.

Contraindications: Use of Integra template is contraindicated in patients with known hypersensitivity to bovine collagen or chondroitin materials. Integra template should not be used on clinically diagnosed infected wounds.

Warnings: Excision of the wound must be performed thoroughly to remove all eschar and nonviable tissue. Integra template will not “take” to nonviable tissue. Leaving any remaining nonviable tissue may create an environment for bacterial growth. Hemostasis should be achieved prior to applying Integra template. Inadequate control of bleeding will interfere with the incorporation of Integra template.

Precautions: There have been no clinical studies evaluating Integra template in pregnant women. Caution should be exercised before using Integra template in pregnant women. Such use should occur only when the anticipated benefit clearly outweighs the risk. In clinical trials, the use of Integra template was evaluated in a small number of patients with chemical, radiation, or electrical burns. A surgeon’s decision to use Integra template on these wounds should be based on their evaluation of the wound and its suitability to excisional therapy, the likelihood that a viable wound bed will be created by excision, and whether the possible benefit outweighs the risk in this patient population. Integra template should be applied on the day of excision. Delays in the application of Integra template may substantially impair the take of the material.

Appropriate techniques to minimize pressure and shearing should be used to reduce risk of mechanical dislodgement. Placing the patient in hydrotherapy immersion may interfere with proper incorporation of the Integra template and cause premature separation of the silicone layer and nonadherence of the template. Caution must be employed to not remove the newly formed neodermal tissue when removing the silicone layer. Integra template must not be excised off the wound. The extent of scarring associated with the use of this product has not been determined.

Adverse Events: Burn Patients: Integra template has been found to be well tolerated in 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 reported in the Integra template clinical trials included death, sepsis, apnea, heart arrest, pneumonia, kidney failure, multi-system failure, and respiratory distress. With the exception of wound fluid accumulation, positive wound cultures, and clinical wound infection, none were directly related to the use 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 six 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 <1% of the safety population.

Adverse events reported in less than 1% of the population were as follows: enlarged abdomen, accidental injury, hypothermia, peritonitis, hypertension, peripheral vascular disorder, arrhythmia, cardiomyopathy, cardiovascular disorder, congestive heart failure, pulmonary embolism, dyspnea, aspiration pneumonia, hypoxia, pleural effusion, respiratory distress syndrome, cholecystitis, gastrointestinal perforation, hepatorenal syndrome, intestinal obstruction, and pancreatitis. 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 35%. The overall infection rate for the Postapproval Study was 16.3%.

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

Integra Bilayer Wound Matrix Brief Summary

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Description: Integra Bilayer Wound Matrix is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. The semi-permeable silicone membrane controls water vapor loss, provides a flexible adherent covering for the wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth.

Indications: Integra Bilayer Wound Matrix is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, pediatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Contraindications: This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials. • The device is not indicated for use in third-degree burns

Precautions: Do not resterilize. Discard all opened and unused portions of Integra Bilayer Wound Matrix • Device is sterile if the package is unopened and undamaged. Do not use if the package seal is broken. • Discard device if mishandling has caused possible damage or contamination • Integra Bilayer Wound Matrix should not be applied until excessive exudate, bleeding, acute swelling and infection are controlled • Debridement or excision must be done thoroughly to remove any remaining necrotic tissue that may cause infection • The following complications are possible with the use of wound dressings. If any of the conditions occur, the device should be removed: infection, chronic inflammation (initial application of wound dressings may be associated with transient, mild, localized inflammation), allergic reaction, excessive redness, pain or swelling.

Omnigraft® Dermal Regeneration Matrix Brief Summary

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Description: Omnigraft is an advanced bilayer for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of bovine collagen and chondroitin-6-sulfate that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Indications: 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.

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. 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.

Adverse Events: All adverse events that were reported in the study evaluating Omnigraft for the treatment of diabetic foot ulcers at a frequency of 1% or in either cohort are presented in Table 1 in the Instructions for Use. This table includes adverse events that were both attributed to and not attributed to treatment. The most common adverse events experienced by patients treated with Omnigraft were: wound infection (15%); new, worsening, or recurring wounds (14%); pain around the wound (9%); infection beyond the wound (either cellulitis or osteomyelitis, 14%); swelling (5%); nausea (5%); worsening health condition (4%). These adverse events occurred in a similar or lower percentage of patients treated with Omnigraft compared to patients treated with standard wound care alone. Omnigraft is also marketed as Integra Dermal Regeneration Template and has been studied extensively in life-threatening thermal injuries and scar contracture reconstruction. Refer to the Integra® Dermal Regeneration Template package insert for complete adverse event information.
References:

Please see products brochures for full indications, contraindications, warnings and precautions, and potential complications.

Availability of these products might vary from a given country or region to another, as a result of specific local regulatory approval or clearance requirements for sale in such country or region.

- Non contractual document. The manufacturer reserves the right, without prior notice, to modify the products in order to improve their quality.
- Warning: Applicable laws restrict these products to sale by or on the order of a physician.
- Consult product labels and inserts for any indication, contraindications, hazards, warnings, precautions, and instructions for use.

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