

HOW SUPPLIED

The sale of INTEGRA template is restricted to clinicians who have completed a company sponsored training program.

INTEGRA template is available in the following sizes:

- 2 inch x 2 inch (5 cm x 5 cm)
- 4 inch x 5 inch (10 cm x 12.5 cm)
- 4 inch x 10 inch (10 cm x 25 cm)
- 8 inch x 10 inch (20 cm x 25 cm)

The bilayer sheets consist of collagen with an outer removable silicone covering identified by black sutures as markers to ensure proper placement on the wound bed. Each sheet of INTEGRA template is stored in phosphate buffer within a foil pouch. Each sterile foil pouch is packaged in a sealed outer chevron-style pouch. Store flat at 2°–30°C. Protect from freezing.

CAUTION: Federal law restricts this device to sale by or on the order of a physician or practitioner with appropriate training.

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.

For product training, please visit www.ilstraining.com.



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INTEGRA[®]
DERMAL
REGENERATION
TEMPLATE



TREATMENT GUIDELINES
Collagen Soft Tissue Technology



Product and Procedure Overview

INTEGRA® Dermal Regeneration Template is a bi-layer skin replacement system designed to provide immediate wound closure and permanent regeneration of dermis. The dermal replacement layer is made of a 3-dimensional porous matrix of cross-linked collagen and glycosaminoglycan. The temporary epidermal substitute layer is made of silicone and functions to control fluid loss and serve as a bacterial barrier. The INTEGRA template is applied following excision of the wound to viable tissue (Procedure #1). Following the regeneration of dermis in about 3 weeks, the silicone layer is removed and replaced by a thin (.004–.008 inch) epidermal autograft (Procedure #2).

These guidelines have been developed based on the collective best practices of experienced users of INTEGRA template. They are intended to be a quick reference to important information on the use of the INTEGRA template and as a supplement to the Physician Training Modules and your unit's own protocols. For additional information contact your Reconstructive Sales Specialist or a Technical Representative at 877-444-1122 or 609-275-9004. For additional product training information and for surgical techniques, visit www.ilstraining.com.

Please note: As the manufacturer, Integra LifeSciences Corporation does not practice medicine and does not recommend any specific technique for use on a particular patient. The physician is responsible for determining and using the appropriate technique for each patient.



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Procedure #1: EXCISION AND APPLICATION

I. Pre-Operative Guidelines

Operating Room Supplies

In addition to standard OR supplies for a burn or reconstructive procedure, the following supplies should be available in the OR:

- Electrocautery instrumentation (i.e., bovie, double plug, bipolar) for pin-point coagulation
- Elastic net dressings if necessary
- Antimicrobial agents/dressings*
- Compression dressings/wraps
- “Non-crushing” Mesher** (if planning to mesh INTEGRA template 1:1); Note: “pie-crusting” is also acceptable
- Splints and brace

* (i.e., Acticoat™ silver impregnated dressing, Sulfamylon® Solution 5%, silver nitrate solution 0.5%)

** A non-crushing mesher refers to a fixed ratio mesher that is known not to crush or tear the matrix. (i.e., Brennen™ Mesher)

Estimating Number of Sheets

Estimate the number of sheets of INTEGRA template you will need available in the OR using the following guidelines and chart:

1. Determine size of area to be covered (i.e., 9% TBSA for an adult or 1750 cm²).
2. Determine product size (i.e., 20 x 25 cm). The following chart provides size suggestions based on anatomical site. If you are planning to mesh the INTEGRA template, it is suggested that you use the 10 x 25 cm (4 x 10 inch) size.
3. Calculate number of sheets by dividing **Surface Area** by **Sheet Area** (i.e., 1750 cm² / 500 cm² = 3.5 sheets).
4. Due to difficulties in estimating surface area and losses due to trimming, it is often advisable to allow for an additional 10% (i.e., 3.5 sheets X 1.10 = 3.85 sheets).

Approximate surface area per sheet of INTEGRA Template

2 x 2 inches = 25 sq. cm.

4 x 5 inches = 125 sq. cm.

4 x 10 inches = 250 sq. cm.

8 x 10 inches = 500 sq. cm.

Estimated number of INTEGRA sheets needed per adult anatomy

Face = 1-2, 8 x 10's

Neck = 2-3, 4 x 10's

Anterior trunk = 4, 8 x 10's and 1-3, 4 x 10's

Posterior trunk = 4-5, 8 x 10's and 1-3, 4 x 10's

Upper extremities = 3-4, 8 x 10' and 1-4, 4 x 10's

Buttocks = 2-4, 8 x 10's

Lower extremities = 4-8, 8 x 10's and 1-6, 4 x 10's

Hands/feet = 1-3, 4 x 10's and 1-3, 4 x 5's

II. Intraoperative Guidelines

Preparing for Application of INTEGRA Template

- Remove all excised tissue and contaminated OR equipment from the sterile patient field before application begins.
- Re-drape area and re-gown as needed. Change gloves before handling INTEGRA template. New sterile instruments are required for INTEGRA placement, shaping and cutting.

Product Preparation

- Fill a basin with 1 liter of sterile saline. The circulating nurse opens the outer Tyvek® pouch. The foil pouch is placed in a sterile field.

Always handle INTEGRA template using aseptic technique.

- On a sterile surface, the foil pouch is peeled open by the scrub nurse.

Note: INTEGRA template is packaged between 2 polyethylene sheets and an attached center tab.

- While holding the tab, gently peel off one of the polyethylene sheets from INTEGRA template.
- Gently peel off the other polyethylene sheet from INTEGRA template
- While holding the tab, the product can now be placed into a basin containing the sterile saline solution. Carefully remove INTEGRA template from the tab.
- Rinse INTEGRA template for 1-2 minutes, Keep the INTEGRA template in the saline bath until application.

Wound Bed Preparation

- Complete excision to viable tissue. Fascia, fat, dermis, muscle and avascular structures are all suitable if the wound bed meets the following requirements:
 - Free from contamination and infection
 - Adequate vascular supply
 - Dry with no signs of bleeding (meticulous hemostasis)
 - Uniform and flat to ensure intimate contact with INTEGRA template
- Prior to placing INTEGRA template, the wound bed may be prepped with a surgical prep/wound cleaner or “Betadine®-type” solution scrub. Do not use Dakins solution to prep the wound bed.

GRAFT BED REQUIREMENTS

Free from contamination and infection:

- Remove all non-viable tissue from wound bed — eschar, necrotic, devitalized and contaminated tissue.
- If wound infection is detected, treat topically and/or systemically according to unit protocols.
- For staged burn excision, it is preferable to have a “zone” between the INTEGRA template and the remaining burn eschar. This “safety zone” should be 2-4 centimeters wide and the excised zone is then covered with one of the following: allograft, xenograft, Biobrane®, Acticoat™, 5% sulfamylon® soaked gauze, 0.5% silver nitrate soaked gauze. The safety zone is left in place until the patient is brought back and the remaining eschar is excised.

Adequate vascular supply:

- Adequate vascular supply is required prior to INTEGRA template application.
- Punctate, uniform capillary bleeding indicates adequate excision of non-viable tissue.
- In certain situations (i.e., obese patients), excising to viable fat may not provide an adequate blood supply.

Dry with no signs of bleeding (meticulous hemostasis):

- Meticulous hemostasis needs to be achieved to prevent hematomas or excessive fluid accumulation.
- To achieve, utilize epinephrine, pinpoint electrocautery, thrombin spray, thrombin-soaked gauze or other topical hemostats. Avoid broad area cauterization which can lead to devitalized tissue.

Uniform and flat wound bed to ensure intimate contact with INTEGRA template:

- Achieve level tissue planes.
- When necessary, marsupialize edges to avoid large step-offs between the wound bed and normal skin.

Meshing INTEGRA Template

If meshing INTEGRA template:

- Use maximum 4 x 10 inch sheets to avoid folding.
- Sheets can be meshed after rinsing.
- Run sheets through a “non-crushing” mesher (i.e. Brennen™ Mesher).
- Handle sheets with gloved hands, do not use instruments.
- Mesh sheets 1:1 but do not expand.

Application of INTEGRA Template

1. Getting Started:

- Silicone side is identified by black threads.
- Start at edge of wound bed.
- Do not allow INTEGRA template to come in contact with un-excised necrotic tissue.

2. Anatomical Site Considerations:

- INTEGRA template may be used on all anatomical sites.
- Joints should be in an un-flexed position.
- Range joints during application to ensure joint mobility and to avoid staple pull-out (i.e., avoid applying sheets too tightly).
- Joints and pressure areas may have an increased risk of mechanical dislodgement.

3. Sheet Placement, Shaping, and Cutting:

- Gently “scoop out” sheets from the holding basin with gloved hands and place directly onto wound bed.
- Do not try to move or “float” sheets like a split-thickness skin graft (STSG). Instead, lift sheets up and reposition.

- There are two basic application techniques:
 - (1) Place sheets on excised wound bed, staple parallel to inside edge of wound bed and trim excess; or
 - (2) Place sheet on excised wound bed, trim sheet to fit site, and staple perpendicular to seam (this allows staples to be placed across seams).
- Cut sheets to avoid gaps and overlaps.
- Place seam lines along Langer's Lines to reduce risk of contracture.
- In a staged procedure, do not place INTEGRA template in contact with unexcised necrotic tissue, rather maintain a safety margin between the excised wound bed and any non-excised necrotic tissue.
- Make sure INTEGRA template lays flat with no wrinkles or bubbles.

4. Sheet Fixation

- Stapling/Suturing
 - Staples or sutures may be used.
 - Fix sheets independently and/or staple adjacent sheets together to minimize gaps, reducing granulation tissue formation.
 - Interrupted stapling (i.e., leaving a 1-2 centimeter space between staples) can be used to seal edges.
- Elastic Net Dressing
 - Place an elastic net dressing over the INTEGRA template site.
 - When applied correctly, the expanded interstices will be open about 1-2 cm and the silicone will have slight indentations from the elastic net dressing.

- The elastic net dressing can be attached by staples or other suitable methods. It will be left in place until the silicone is removed.

5. Dressing the INTEGRA Template in the OR

- Build dressings in layers. Each layer has an important function:
 1. Fixation Layer — Elastic net dressing for intimate contact.
 - a. Compression Layer — Compression bandage for protection and anti-shear properties.
 - b. Bulky Dressing Layer — Bulky gauze for protection and antimicrobial retention.
 2. Anti-Shear (Optional) — An additional anti-shear layer is sometimes used.
- Antimicrobial Layer — Acticoat™, Silver Nitrate 0.5% or Sulfamylon® Solution 5% soaks to prevent infection.
- Do not let Dakins Solution, petroleum-based products (i.e., Xeroform), or enzymatic debridement agents (i.e., Collagenase), come in contact with the INTEGRA template grafted sites.
- Use splints or bolsters, per unit protocols, during first 5-7 days. Splints should be applied in the OR and should stay on at all times (except when performing wound care).
- The V.A.C.® System (Vacuum Assisted Closure) may be used over unmeshed or meshed INTEGRA template sites, in particular, as a bolster dressing for difficult anatomical sites or wound beds, such as the axilla.

III. Post-Operative Care Guidelines

Dressing Changes

- Dressings should be changed approximately every 2-3 days, or more often based on patient's condition.

Inspection

- If an elastic net dressing is used, do not remove staples/sutures.
- Take down all dressings to inspect INTEGRA template sites, seams, and edges for evidence of hematomas, fluid accumulation, infection/purulence, premature silicone layer separation, and areas of non-take. Inspection may be performed through interstices of elastic net dressing-do not remove unless necessary.
- Remoisten antimicrobial dressings after INTEGRA template inspection.
- Remoisten or reapply antimicrobial dressing as needed, typically every 6-8 hours, or more often for dry climates.
- Replace or change new antimicrobial dressings at least every three days.

Positioning and Moving the Patient

- The goal when positioning or moving the patient is to minimize shear forces on INTEGRA template sites.
- Common methods used to move the patient include log rolling, use of bed sheet to position patient, use of board to move patient, and use of plastic-coated surfaces (i.e., plastic bag, Mayo Stand cover) designed to reduce friction on the INTEGRA template.
- When using your hands to move patient, care should be taken to reduce stress on the INTEGRA template.
- If the INTEGRA template is used on the back, place patients in prone position. Care should be used when Integra is on a location

that may receive pressure (ie. back).

- Use of air fluidized, intermittent zero pressure specialty beds, or low air loss beds may be appropriate.

Physical Therapy/Occupational Therapy

- Range of motion exercises can be started on Post-operative day (POD) 5-7.
- Gentle range of motion (ROM) exercises can begin between POD 5-7, progressing according to your PT/OT's protocol. If complications have delayed healing or the INTEGRA template sheets are not firmly adhered to the wound bed, delay ROM accordingly.
- The decision to remove bulky dressings, bolsters or splints to perform ROM exercises must be made on a case-by-case basis under consultation with PT/OT.
- Care must be taken during PT/OT to minimize the risk of shearing.

Neodermis Formation

- Beginning POD 1 and extending to POD 14 to 28 or longer, the appearance of the INTEGRA template or neodermis will vary. The rate and progression of the color change depends on the patient and rate of healing.
- Generally, neodermis color will change through a progression from red to pink to orange/peach to vanilla.
- Neodermis must be inspected for darkened areas or white/gray areas which may result from complications (see Complications and Interventions for more info on how to recognize and treat).
- Silicone is typically ready for removal around POD 21 (possibly sooner with use of V.A.C.® System); signs that neodermis formation is complete include:
 - Neodermis blanches to the touch; and returns to previous

color indicating capillary refill.

- Silicone wrinkles and may begin to detach from the neodermis.
- Granulation tissue (deep red color and granular surface that bleeds easily) has formed at seam lines.

Complications and Interventions

Hematoma POD 0-3 (See pictures on page 37)

Hematomas usually develop in the first 48 hours. Hematomas need to be removed and any bleeding/drainage must be stopped to allow cellular ingrowth into the matrix.

- If hematoma is still in fluid state: evacuate hematoma by inserting an 18-20 gauge hollow point needle with syringe or cotton tip applicator under surface of INTEGRA template and aspirate fluid.
- If hematoma is no longer in fluid state: incise INTEGRA template with a #15 blade, then evacuate clot using a gentle rolling motion with a sponge or tongue blade, or use cotton tip applicator to remove hematoma.
- Control drainage/bleeding by irrigating with diluted epinephrine and reattaching INTEGRA template.
- For a large, persistent hematoma or continued bleeding:
 - Remove necessary staples
 - Lift INTEGRA template using the blunt end of forceps
 - Remove clot
 - Obtain hemostasis with epinephrine, electrocautery, or surgical ligature
 - Return the INTEGRA template gently to original position and re-secure

Fluid Accumulation POD 1-5 (See picture on page 38)

In unmeshed INTEGRA template sheets, clear or amber fluid may accumulate under the matrix. Although fluid drainage is a normal part of the healing process, fluid accumulation can lead to infection and/or formation of granulation tissue and should therefore be removed.

Evacuate by aspirating, rolling or “wicking” with a cotton-tip applicator or gauze pad an 18-20 gauge hollow point needle with syringe or cotton tip applicator under surface of INTEGRA template and aspirate fluid.

Purulence/Infection POD 0-12 (See picture on page 39)

Infection is the most common cause for loss of INTEGRA template. Common sources are non-viable tissue in the wound bed, or contamination through seams or staple holes. If purulence and infection are promptly dealt with, loss of INTEGRA template sheets can be avoided.

- Remove all signs of possible purulence irrigate, then
 - Aspirate or evacuate by incising/rolling
 - Treat with topical antimicrobials — Irrigate INTEGRA template sites at seams/edges and beneath the silicone layer with a topical antimicrobial such as Sulfamylon® 5% solution/slurry, G-U irrigant, or silver nitrate 0.5% solution. Irrigate frequently (2-6 times daily)
 - Culture and initiate systemic antibiotic therapy
- If aggressive treatment of purulence is not successful as evidenced by increasing purulence/pus, non-take of INTEGRA template (i.e., a “floating” sheet) or silicone separation, then the affected area needs to be removed.
 - Remove only the affected area using a “windowing” (remove silicone over area to be treated, creating a “window” effect), treat with topical antibiotics.
 - Treat as open wound until infection is resolved. Once infection is resolved, apply new INTEGRA template sheet or treat with temporary covers (i.e., allograft) until ready to autograft. If new INTEGRA sheet is applied then, at time of epidermal autograft, the granulation tissue should be removed, revealing neodermis underneath ready for grafting.

Areas of Incomplete INTEGRA Template Take (i.e., inadequate neodermis formation) POD 5 or higher

Areas of incomplete take or detachment of the INTEGRA template can result from mechanical dislodgement (due to shear, improper splinting, PT), infection, hematoma, premature silicone separation or damaged matrix.

- There are several options for treating areas of incomplete take

depending on the size of the area, the amount of neodermis formed and timing (i.e., POD).

- Areas under 2 sq. cm. should be monitored for infection but not removed until time of epidermal grafting.
- Areas over 2 sq. cm. should be removed and treated by either (1) reapplication of new INTEGRA template or (2) STSG.
- Identification of poor INTEGRA template take is identified by poor color and lack of adherence (lateral movement of matrix under finger pressure).

Premature Silicone Separation POD 1-21

The silicone layer can be left in place for extended periods without detrimental affects to the underlying neodermis. Premature separation of the silicone is not a problem if it stays in contact with the neodermis.

• Early Silicone Separation POD 1-9

- Inspect wound for signs of shearing, fluid collection, hematoma, or infection. Detect loose areas of INTEGRA template by using your finger to slide loose silicone.
- Remove the source of the separation and re-attach.
- If the INTEGRA template is engrafted with evidence of neodermis, then cover exposed neodermis with allograft, xenograft, or epidermal autograft to prevent desiccation.

• Late Silicone Separation POD 10 or higher

- Remove source of non-adherence. Remove silicone if unable to re-secure. Apply new non-adherent if silicone becomes soiled or completely separated.
- If INTEGRA template is not engrafted and there is no evidence of neodermis, remove and replace with new INTEGRA template and/or other graft material.
- If INTEGRA template is engrafted, then cover with allograft, xenograft or epidermal autograft to preserve the neodermis.
- In the event that the silicone layer becomes detached, gently

remove the silicone from the Integra matrix and discard the silicone layer. Place a new non-adherent dressing gently over the Integra matrix prior to replacing the outer dressing.

Procedure #2: SILICONE REMOVAL AND EPIDERMAL AUTOGRAFTING

Planning for Epidermal Grafting

- Prior to removal of silicone, assess availability of donor sites:
 - Estimate size of epidermal graft, based on amount of tissue required.
 - Do not remove and expose more neodermis than expanded epidermal graft will cover. The silicone layer may be left in place for extended periods if the staging of the epidermal autograft procedure is required.

Removal of Silicone

- Remove staples or sutures.
- Use forceps to gently remove silicone; while lifting from edges, peel back carefully (use spatula or blunt instrument to separate if necessary).
- Difficult separation may indicate that neodermis has not fully matured.

Inspect and Prepare the Neodermis

- Inspect the neodermis carefully.
Remove the following:
 - Any excessive granulation tissue at seams, edges, interstices and staple sites.

- Any necrotic tissue.
- Areas of incomplete take.
- Prepare a flat, clean surface using scalpel, scissors, or curettes.
- In preparation for skin graft placement lightly debride the surface of the neodermis with a gauze pad or surgical scrub brush.
- Although neodermis does not bleed easily, if bleeding occurs, control bleeding with an epinephrine-soaked gauze pad.

Harvesting the Thin Epidermal Autograft

- Expand the site by infusing with saline to facilitate harvesting.
- Harvest a thin epidermal autograft at approximately 0.006 inches:
 - Grafts taken thinner than 0.004 inches may result in the poor engraftment due to an insufficient transfer of the basement membrane.
 - Grafts taken thicker than 0.008 inches may result in a residual meshed appearance (if meshing) or a greater risk of donor site scarring.

Placing the Epidermal Graft

- Place and attach the epidermal graft according to unit protocols.
- Thin epidermal grafts are more fragile than conventional STSG, making handling more difficult:
 - Thinness of graft makes orientation easy to confuse (curl under indicates correct orientation).
 - Use saline to float graft into position.
 - Interstices should be of uniform size and no more than 2 millimeters.

Epidermal Autograft Dressings and Care

- Dress the donor site per surgical unit protocol.

- Dress and care for epidermal graft sites using the protocols typically used for thick split-thickness skin grafts.
- Similar to dressing INTEGRA template sites, build dressings in layers and immobilize joints in a flexed position.
- Change dressings every third day, unless positive cultures require daily changes.
- If the epidermal graft seems to “disappear”, obtain cultures. In some cases, this is typically the result of the graft being too thin or the presence of infection:
 - If negative, continue to dress normally. Engraftment and confluence should occur within 21 days.
 - If positive, administer antibiotics and continue to monitor closely.

NOTE: Certain locations, such as the bottom of the foot or hand, are exposed to increased levels of pressure and general wear; therefore, they have an increased risk of injury and breakdown. Due to this, an epidermal graft greater than 0.008 inches may be needed.

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Tyvek is a registered trademark of E.I. duPont.

V.A.C. is a registered trademark of KC1 Licensing, Inc.

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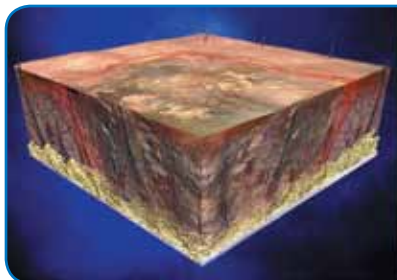


APPENDIX

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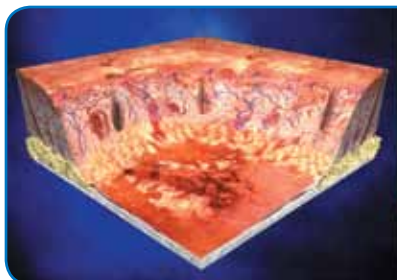
Clinical Sequence



Burn Injury



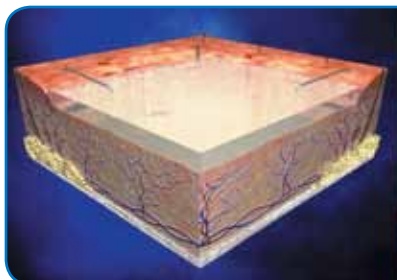
Day 0



Excised Bed



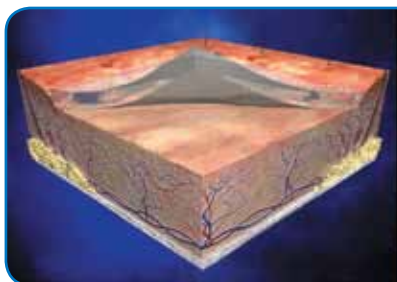
Day 1



Neodermis Formation



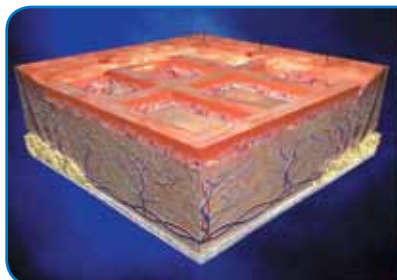
Day 6



Silicone Removal



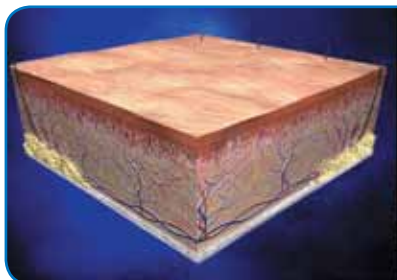
Day 21



Epidermal Graft



Day 21



Regenerated Skin

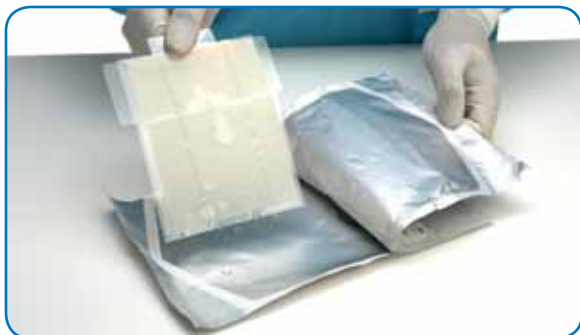


Day 30+

Product Preparation



On a sterile surface, peel open package



Remove product from package



While holding tab, gently peel one of polyethylene sheets from product

**Gently peel
off other
polyethylene
sheet**



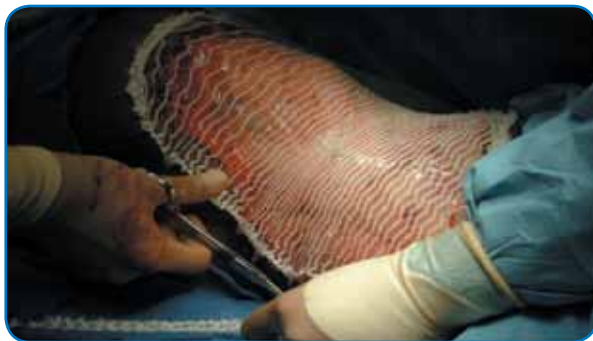
**While holding
tab, place
product in
sterile saline
basin**



**Carefully
remove tab
from product
and rinse for
1-2 minutes**



Dressing Regimen



A. Fixation layer



B. Antimicrobial layer

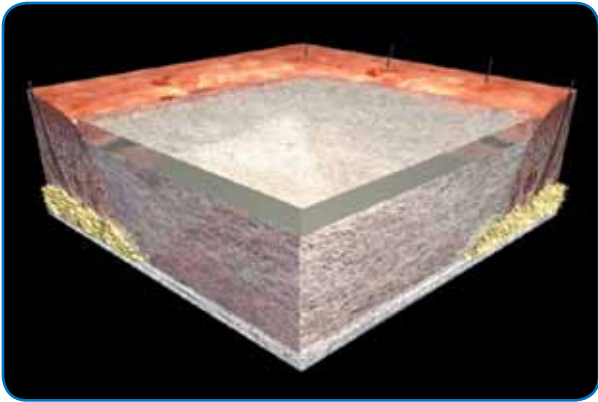


C. Lap pad layer



D. Compression layer

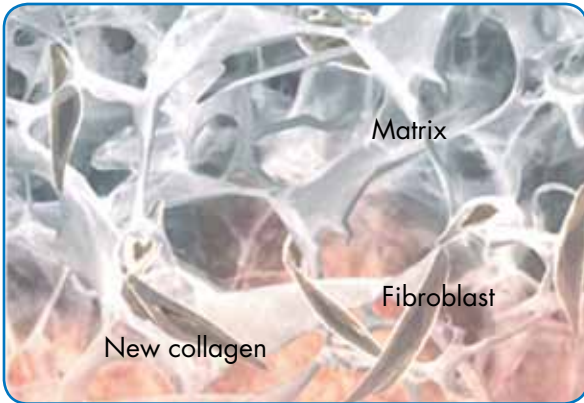
Dermal Regeneration



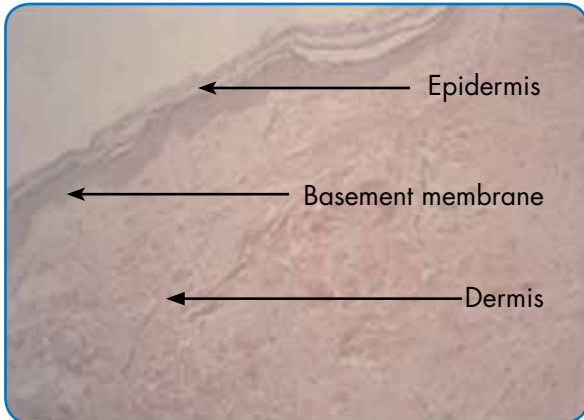
Neodermis Formation



Engraftment and confluence of the epidermal graft complete the process



Cellular infiltration of matrix



Histology of neodermis following silicone removal at 21 days

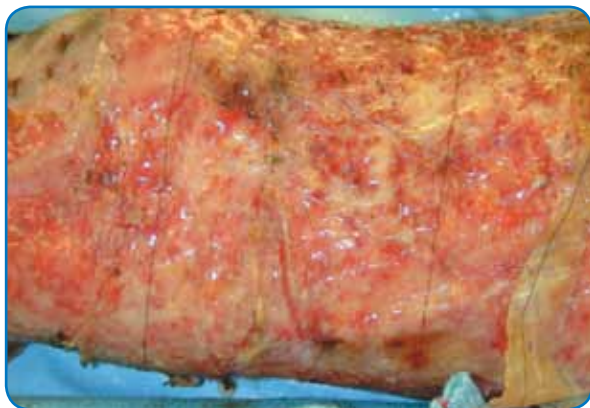
Neodermis Maturation



Day 0



Day 7



Day 14



Day 21

Silicone Removal and Epidermal Grafting



Removal of silicone layer



Using dermatome to harvest thin epidermal autograft from donor site



Application of thin epidermal autograft



Fixation of epidermal autograft

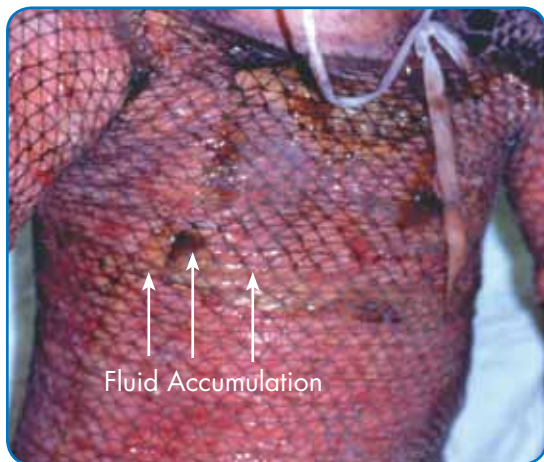
Large Hematoma



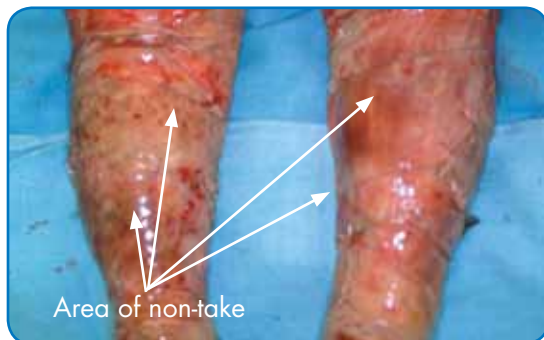
Small, Late-Forming Hematoma



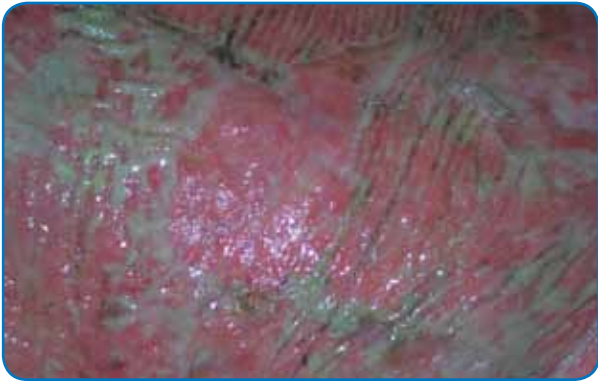
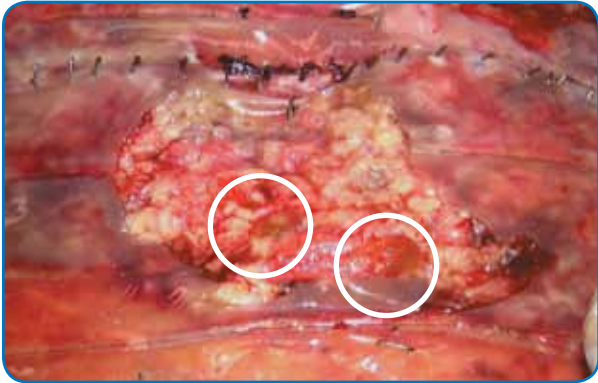
Fluid Accumulation



Non-Take of INTEGRA Template



Infection



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 coagulation 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 must 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. Delaying 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 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 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 $\leq 1\%$ of the safety population.

Incidence of adverse events occurring in $\geq 1\%$ of the safety population in the Post-approval Study are as follows:

Adverse Events	n/N (%)
Sepsis	50/216 (23.1%)
Death	30/126 (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, gastrointestinal perforation, hepatorenal syndrome, intestinal obstruction, and pancreatitis.

Adverse events reported in the INTEGRA template clinical trials included death, sepsis, apnea, heart arrest, pneumonia, kidney failure, multisystem 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.

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%.

CONTRACTURE RECONSTRUCTION PATIENTS

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

Incidence of Adverse Events in the Reconstructive Contracture Surgery Study and Retrospective Contracture Reconstruction Survey

	Reconstructive Surgery Study N = 30 Sites	Retrospective Contracture Reconstruction Survey N = 127 sites
Adverse event	n/N (%)	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.