Medicare Appeal Packet for Integra® Dermal Regeneration Template

As a service to our customers, Integra LifeSciences Corporation has assembled this packet of information to assist with the Medicare appeal process. Included in this packet are as follows:

- Information on how to appeal a Medicare Claim Determination
- Sample Letter of Medical Necessity
- Sample Statement of Medical Necessity
- Package Insert
- FDA Approval Letter
- Bibliography of clinical articles relative to the Integra™ Matrix Family of Products

If you would like to obtain clinical articles to help support the appeal, please contact Customer Service at 1-877-444-1122, Option 1. Please have readily available, the specific Integra™ product that is being appealed in order for Customer Service to provide you with the relevant clinical literature. Thank you.

ER4310 – 10/10

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609-275-0500 ▪ 800-654-2873 toll free ▪ 609-750-4277 fax ▪ integralife.com

Appealing a Claim Determination

General Information:

Individuals enrolled in Medicare may file an appeal if they believe Medicare should have paid for, or did not pay enough for, an item or service that they received. An individual's appeal rights are on the back of the Medicare Summary Notice (MSN) mailed to Medicare beneficiaries after they receive services. The MSN explains why a bill was not paid and how to file an appeal. The providers and suppliers of services that file claims on behalf of Medicare beneficiaries may also file appeals.

The Medicare Part B Fee-for-Service Appeals Process:

Appeal Type	Time Limit for Filing Request	Monetary Threshold to be Met
Redetermination (submitted to Part B contractor) ***http://www.cms.hhs.gov/cmsforms/downloads/cms20027.pdf***	Within 120 days of receipt of the notice of initial determination	None
Reconsideration (submitted to a Qualified Independent Contractor QIC) ***http://www.cms.hhs.gov/cmsforms/downloads/cms20033.pdf***	Within 180 days from the date of receipt of the notice of the redetermination	None
Administrative Law Judge Hearing (ALJ)	Within 60 days after receipt of the reconsideration notice	Minimum of $120
Departmental Appeals Board (DAB) Review	Within 60 days from the date of receipt of the ALJ decision	None
Federal Court Review	Within 60 days from the date of receipt of the DAB's decision	Minimum of $1180

Documentation to include with your Appeal request:

In an effort to present a solid case to Medicare or any other insurance carrier that the use of Integra® Dermal Regeneration Template was/is in the best interest of the patient, it is important to submit with the appeal, pertinent health information pertaining to the treatment of the wound. Examples of relevant information to include would be:

- History and Physical documentation
- Progress/Office notes specific to the treatment of the wound
- Operative Reports specific to the treatment of the wound
- Pictures of the wound
- Documentation that may illustrate previous wound treatments

Letter of Medical Necessity

If a procedure was deemed by the insurer as "not medically necessary," it may be required that you prove medical necessity as part of your appeal. In addition to providing relevant health information specific to the treatment of the patient's wound, a Letter of Medical Necessity should accompany the appeal to help further justify the use of Integra® Dermal Regeneration Template.

If a Letter of Medical Necessity has been requested, we have available a sample letter, as well as a sample template (on the following two pages) to assist you in the process. Also available, upon request, Integra LifeSciences Corporation can provide you with clinical articles to help support your claim. Please feel free to contact our Customer Service department at 1(877) 444-1122 option 1, and they will FedEx a packet of clinical articles to you ASAP.

For more information regarding Medicare, please go to http://www.cms.hhs.gov/

** Integra has used reasonable efforts to provide accurate coding advice, but this advice should not be construed as providing clinical advice, dictating reimbursement policy or substituting for the judgment of a practitioner. Integra LifeSciences Corporation assumes no responsibilities or liabilities for the timeliness, accuracy and completeness of the information contained herein. Since reimbursement laws, regulations and payor policies change frequently, it is recommended that providers consult with their payors, coding specialists and/or legal counsel regarding coverage, coding and payment issues.

Sample Letter of Medical Necessity:

Sample Letter of Medical Necessity
(Please type on physician's letterhead)

Date:

<< Insurance Company>>
<<Address>>
<<City, State, Zip Code>>

Re: <<Patient's Name>>
Policy Number: << xxxxxx>>
Group Number <<xxxxxx>>

To Whom It May Concern:

Enclosed for your review, are clinical articles documenting the effective use of Integra® Dermal Regeneration Template. The attached Statement of Medical Necessity and information pertaining to <<Patient's Name>> clinical history and diagnosis clearly demonstrate that Integra® Dermal Regeneration Template is the treatment of choice.

Please send me written verification of coverage and payment for the procedure noted for <<Patient's Name>> as soon as possible. If you have any questions pertaining to the clinical history or my treatment plan, please call me directly at:

<<Office Phone Number>>

Thank you for your immediate attention to this matter.

Sincerely,

<<MD's Name>>

Enclosure: Statement of Medical Necessity
Estimate of Professional and Facility Charges
Patient Records

CC: <<Patient Name>>
Medical Record File
<<Facility billing contract>>

Sample Statement of Medical Necessity for Proposed Procedure Utilizing Integra® Dermal Regeneration Template

PATIENT NAME: _____ GENDER: M or F

ADDRESS: _____ DATE OF BIRTH: _____

_____ FACILITY NAME: _____

PHONE: _____

INSURANCE CO: _____ SUBSCRIBER: _____

GROUP NAME: _____ DATE OF DIAGNOSIS: _____

DIAGNOSIS: _____

ICD-9 DIAGNOSIS CODE(S): _____ SIZE OF WOUND: _____

ETIOLOGY OF WOUND: _____ DATE OF DIAGNOSIS: _____

DETAILED DESCRIPTION OF WOUND: _____
_____
_____

OTHER MEDICAL CONDITIONS: _____
_____

TREATMENT PLAN: _____
_____

MEDICAL NECESSITY OF USING INTEGRA® DERMAL REGENERATION TEMPLATE FOR THIS WOUND: _____
_____
_____
_____

PHYSICIAN NAME: (please print) _____

ADDRESS: _____

PHYSICIAN SIGNATURE: _____ DATE: _____

INTEGRA® DERMAL REGENERATION TEMPLATE

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® 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.

INTEGRA® Dermal Regeneration 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 for 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 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.

Incidence of adverse events occurring in ≥1% of the safety population in the Postapproval Study are as follows:

Adverse Events	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, gastrointestinal perforation, hepatorenal syndrome, intestinal obstruction, and pancreatitis.

Adverse events reported in the previous studies are as follows:

Coded Symptom	Multicenter N=149 (% frequency)	Anatomic Site N=59 (% frequency)	Meshed vs Sheet N=20 (% frequency)
Death	37 (24.8%)	19 (32.2%)	3 (15%)
Sepsis	17 (11.4%)	4 (6.8%)	1 (5.0%)
Apnea	13 (8.7%)	5 (8.5%)	0 (0.0%)
Pneumonia	10 (6.7%)	0 (0.0%)	0 (0.0%)
Heart Arrest	7 (4.7%)	6 (10.2%)	0 (0.0%)
Kidney Failure	5 (3.4%)	4 (6.8%)	0 (0.0%)
Respiratory Distress	3 (2.0%)	0 (0.0%)	0 (0.0%)
Infection	2 (1.3%)	0 (0.0%)	0 (0.0%)
Lung Disease	2 (1.3%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (0.7%)	1 (1.7%)	0 (0.0%)
Adrenal Insufficiency	1 (0.7%)	0 (0.0%)	0 (0.0%)
Agitation	1 (0.7%)	0 (0.0%)	0 (0.0%)
Convulsion	1 (0.7%)	0 (0.0%)	0 (0.0%)
Hematemesis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Hemoptysis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Liver Cirrhosis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Nonadherence	1 (0.7%)	0 (0.0%)	0 (0.0%)
Shock	1 (0.7%)	0 (0.0%)	0 (0.0%)
Skin Discoloration	1 (0.7%)	0 (0.0%)	0 (0.0%)
Asystole	0 (0.0%)	0 (0.0%)	1 (5.0%)
Cerebral Artery Infarct	0 (0.0%)	1 (1.7%)	0 (0.0%)
Metastatic Ovarian Cancer	0 (0.0%)	1 (1.7%)	0 (0.0%)
Peritonitis	0 (0.0%)	1 (1.7%)	0 (0.0%)
Sarcoidosis	0 (0.0%)	0 (0.0%)	1 (5.0%)
Third Degree Burn	0 (0.0%)	1 (1.7%)	0 (0.0%)
Multisystem Failure	0 (0.0%)	3 (5.1%)	0 (0.0%)

With the exceptions 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 Contracture Reconstruction 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.

SUMMARY OF CLINICAL STUDIES

Burn Patients

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

- Multicenter 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.

Data Across Studies

Variable		Multicenter Study	Anatomical Site Study	Meshed vs. Sheet Study	Postapproval Study
Year		**1983-1989**	**1985-1992**	**1989-1992**	**1997-2000**
Number of Patients		149	59	20	216
Number of Wound Sites		207	130	59	841
Age:	(Mean ± SD) Range	32.0 ± 21.5 <1 – 88Y	49.2 ± 21.2 19 – 93Y	30.1 ± 15.6 4 – 59Y	34.7 ± 23.9 4 M – 87Y
Gender:	Male	112 (75.2%)	33 (55.9%)	16 (80%)	151 (69.9)%
	Female	37 (24.8%)	26 (44.1%)	4 (20%)	65 (30.1%)
Race:	Caucasian	98 (65.8%)	56 (94.9%)	14 (70.0%)	151 (69.9%)
	Black	32 (21.5%)	0 (0.0%)	6 (30.0%)	38 (17.6%)
	Hispanic	15 (10.1%)	3 (5.1%)	0 (0.0%)	20 (9.2%)
	American Indian	3 (2.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Asian	1 (0.7%)	0 (0.0%)	0 (0.0%)	4 (1.8%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
% BSA Total Burn:	(Mean ± SD) Range	45.7 ± 18.6 14.5 – 88.5	49.8 ± 24.6 1 – 97	53.6 ± 19.4 30 – 90	36.5 ± 24.7 <1 – 95
% BSA Full-Thickness:	(Mean ± SD) Range	31.8 ± 20.8 0 – 88.5	42.5 ± 24.0 1 – 95	35.4 ± 22.4 0 – 78	27.9 ± 24.4 0 – 95
% Inhalation Injury		42%	62.5%	50%	45%
Mean Take		65.1%*	77.6%	80.6%	76.2%
Median Take		80%*	95%	100%	98%
Infection		55%	14%	25%	16.3%
Mortality		24.8%	32%	15%	13.9%

**paired comparative wound sites.*

Multicenter Safety and Efficacy Clinical Trial (Pivotal Study)

In the pivotal multicenter clinical trial, 149 patients 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 multicenter 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 multicenter 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 multicenter 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 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.

SUMMARY OF CLINICAL STUDIES
Contracture Reconstruction Patients

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 were: 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

INTEGRA template facilitates the formation of a neodermis by the body. The collagen dermal portion serves as a template for the infiltration of fibroblasts, macrophages, lymphocytes, and capillary endothelial cells which form the neovascular network. As healing progresses, the collagen-GAG layer is resorbed and new collagen is deposited by the fibroblasts to form the neodermis. Upon adequate vascularization of the neodermis and the availability of the donor autograft, the silicone layer is removed and a thin, meshed layer of epidermal autograft is placed over the neodermis. Cells from the epidermal autograft grow and form a mature epidermis thereby closing the wound, and resulting in a functional dermis and epidermis.

Patient Evaluation and Selection of Sites for Application of INTEGRA Template

As the extent of the patient's thermal injury is evaluated, all burn areas requiring prompt excision and grafting should be identified. INTEGRA template may be applied to all excised wound sites.

SURGICAL APPLICATION

Scheduling Surgery for INTEGRA Template Application

INTEGRA template must be applied to a viable wound bed following surgical excision of burn wounds. Surgery may be scheduled as soon as the patient is stabilized. Surgery should be staged as appropriate.

Perioperative Antibiotics

Perioperative antibiotics are recommended to be administered according to the clinical judgment of the practitioner.

Product Preparation

1. Always handle INTEGRA template using aseptic technique.
2. Peel open the outer pouch and remove the inner foil pouch using sterile technique.
3. Place foil pouch flat on a sterile surface and peel it open.
4. Remove product, including the protective polyethylene cover sheets.
5. While holding the product with the tab, remove one polyethylene cover sheet. Turn the product and remove the second polyethylene cover sheet.
6. Using the tab, the product can now be placed into a basin containing sterile saline solution. Carefully remove the tab from the product.
7. Rinse the product by immersion in sterile saline for 1–2 minutes.
8. Keep product in the basin until application.

Meshing INTEGRA Template

INTEGRA template can be meshed at 1:1 ratio before the application, but must not be expanded. Meshing may improve the ability of INTEGRA template to conform to irregular surfaces and may improve take on exudating wounds.

Wound Excision

Excision must be made to the level of viable tissue and meticulous hemostasis must be achieved before application of INTEGRA template.

Excisional techniques for INTEGRA template sites can be fascial, sequential, or tangential. It is absolutely critical to the successful take of INTEGRA template that excision be complete and that no devitalized tissue remains.

Complete hemostasis must be achieved before application of INTEGRA template. The presence of hematoma will cause loss of INTEGRA template in the affected area. Broad area cauterization that could decrease wound bed viability should be avoided.

Shaping INTEGRA Template to Fit the Wound

INTEGRA template should be shaped accurately to fit the excised wound margins to minimize scarring at these margins. It should not be overlapped onto non-excised areas or onto other sheets of INTEGRA template. It is easily cut with sterile scissors by placing the sheet of INTEGRA template over the excised wound bed and cutting exactly to the edge.

Applying INTEGRA Template to the Wound

It is critical that the collagen template layer be in direct contact with the excised wound. The silicone layer (identified by the black threads) must be placed out (away from the wound bed). Do not apply upside down, the black threads must be clearly visible.

For optimal cosmetic results, place the INTEGRA template so that the suture lines between INTEGRA template sheets lie in Langer's lines. This will minimize the final appearance of the suture lines.

The INTEGRA template sheets are secured by staples or sutures placed in an interrupted fashion under slight tension. If the INTEGRA template has been meshed, care must be taken not to spread the mesh. Care should be taken to achieve a primary closure between INTEGRA template and adjacent unburned skin or between sheets of INTEGRA template. Suture or staple each sheet of INTEGRA template in place independently. The INTEGRA template sheets may also be affixed to one another to assure that there is no gap between sheets. Adjust the area to ensure that there is no undue tension on an individual piece of INTEGRA template. The material should readily adhere and conform to the wound surface. Any air bubbles should be carefully removed by moving them to the edge of the sheet. Dressings should be applied over INTEGRA template according to the protocol of the practitioner.

Postoperative Care

Postoperative care, like that used following treatment with full sheet or meshed autograft, should include monitoring for hematomas, wound infection and patient sepsis.

The outer dressing should be changed as necessary. However, the inner dressing need not be disturbed unless there are problems requiring intervention. The attachment of the silicone layer should be examined. An antibacterial dressing may be used or the outer dressing can be soaked in an appropriate antimicrobial solution.

There should be no hydrotherapy immersion of the patient following INTEGRA template application while the silicone layer is in place.

Mechanical dislodgment of INTEGRA template should be avoided. Ambulation and physical therapy can be instituted according to the condition of the patient and judgment of the practitioner. All INTEGRA template sites must be securely covered with dressings before ambulation and/or physical therapy.

Staples or sutures should remain in place until the time of epidermal autografting. The staples or sutures help secure the silicone layer and decrease the likelihood of premature silicone layer separation.

EPIDERMAL AUTOGRAFTING

Identifying the Neodermis

The area of INTEGRA template take (neodermis formation) should be evaluated before application of the epidermal autograft. Neodermis may be recognized by a yellow-orange color with occasional areas of light red. The neodermis should be firmly attached to the underlying tissue. The silicone layer should easily separate from the underlying neodermis.

Removal of Silicone Layer for Epidermal Autograft

The silicone layer of INTEGRA template may be removed when the collagen layer has been replaced by neodermis, usually 14 to 21 days after application of INTEGRA template. Removal of the silicone layer and grafting may take place immediately after formation of the neodermis, if epidermal autograft is available. The removal of the silicone layer may be postponed until donor sites for epidermal autograft area are available.

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 neodermis formation is incomplete. However, if the silicone is difficult to remove, a forceps and scalpel may be used to gently separate the silicone layer from the neodermis. 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.

Harvesting and Preparation of the Epidermal Autograft

Epidermal autograft can be taken from sites unsuitable for conventional autograft, for example small areas from which a large intact sheet would be impossible. If possible, the area should be matched for color and type of skin.

A thin epidermal autograft should be taken at a thickness just sufficient to provide punctate bleeding of the donor site, typically 0.004–0.006 inches (0.10 mm–0.14 mm). Dermal tissue is not needed in the epidermal autograft, and should be minimized.

Typically, the thin epidermal autograft may be meshed up to a 4:1 ratio. The meshed epidermal autograft may be fragile and care should be taken in handling the graft.

Application of the Epidermal Autograft to the Neodermis

The epidermal autograft should be placed over the neodermis by spreading the meshed autograft. It should be spread as evenly as possible over the neodermis without leaving large open areas.

Completion of the epidermal autograft procedure should follow the standard protocol for full sheet or meshed autograft. The epidermal autograft should be anchored by sutures or staples. The dressing over the epidermal autograft should be similar to that used over conventional meshed autograft.

POTENTIAL POSTOPERATIVE PROBLEMS

Wound Colonization or Infection

Wounds having excessive discharge may require more frequent dressing changes and may require the use of appropriate antimicrobial intervention. After a diagnosed infection is controlled, either INTEGRA template or a thin epidermal autograft may be applied.

Patient Sepsis

The dressings should be removed and wound sites inspected for infection (INTEGRA template or autograft). Appropriate diagnostic and therapeutic procedures should be followed.

Hematoma

Areas of hematoma should be monitored and aspirated or excised as required. New INTEGRA template or autograft may be applied to the excised sites.

Poor Take of INTEGRA Template

If INTEGRA template is not incorporated into the wound bed, carefully remove the INTEGRA template and examine the wound bed. Areas of poor INTEGRA template take may be treated by reapplication of INTEGRA template or by application of conventional autograft.

Fluid Accumulation and Premature Silicone Layer Separation

Fluid accumulation or premature silicone layer separation must be treated to prevent infection or granulation tissue. Small areas of fluid accumulation under the silicone layer may be aspirated and cultured. If the silicone layer separates from the wound bed after neodermis formation begins, only the loose area of the silicone layer need be removed.

Inflammation

INTEGRA template grafts do not become inflamed unless there is a bacterial complication. This should be treated based on the clinical judgment of the practitioner.

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.

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 reuse after opening		Sterile. Method of sterilization: irradiation
	See instructions for use		Expiration date
	Federal (USA) law restricts this device to sale by or on the order of a physician or practitioner		Product complies with requirements of directive 93/42/EEC
	Lot number		Store between 2° - 30°C
	Authorized Representative in the European Community		Manufacturer holding CE mark

FDA APPROVED

Integra LifeSciences Corporation
311 Enterprise Drive, Plainsboro, New Jersey 08536

RMS# 76000-1200-0

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 19 2002

Ms. Judith O'Grady, R.N., MSN, RAC
Senior Vice President, Regulatory Affairs
Quality Assurance and Clinical Affairs
INTEGRA LifeSciences Corporation
311C Enterprise Drive,
Plainsboro, NJ 08536

Re: P900033/S8
INTEGRA ® Dermal Regeneration Template
Filed: October 26, 2001
Amended: November 20 and December 19, 2001, March 13 and 26, and April 18 and 19, 2002

Dear Ms. O'Grady:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the INTEGRA Dermal Regeneration Template. This device 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 Dermal Regeneration 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." The PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at one year at 35°-46° F (2°-8°C).

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

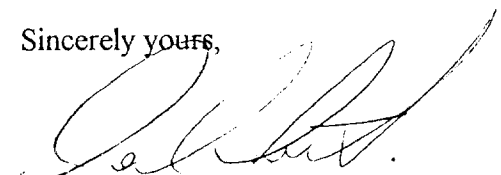
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact D. Laurie Bernato at (301) 594-3090, ext. 132.

Sincerely yours,



Daniel Schultz, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

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POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

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3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.
The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

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