Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name: Interactive Wound Dressing

Device Trade Name: INTEGRA® Dermal Regeneration Template

Applicant: Integra LifeSciences Corporation
311 Enterprise Drive
Plainsboro, NJ 08536, USA

PMA Number: P900033

Supplement Number: S008

Date of Notice of Approval: April 19, 2002

II. Intended Uses/Indications

INTEGRA® Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient. Written requests for a copy of the Summary of the Safety and Effectiveness Data for this indication can be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

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.

III. Device Description

INTEGRA® Dermal Regeneration Template (INTEGRA template) is a bilayer membrane system for skin replacement. The dermal replacement layer is made of a three-dimensional porous matrix of fibers of cross-linked bovine tendon collagen and a glycosaminoglycan (GAG) (chondroitin-6-sulfate) that is manufactured with a controlled porosity and defined degradation rate. The temporary epidermal substitute layer is made of synthetic polysiloxane (silicone). The silicone layer provides immediate wound homeostasis by controlling moisture flux from the dermis in a manner comparable to normal skin and imparts strength to the INTEGRA template.

The collagen-GAG dermal layer of INTEGRA template functions as a biodegradable template that induces organized regeneration of dermal tissue ("neodermis") by the body. The pore volume fraction, average pore size, and degradation rate of the collagen-GAG dermal layer are

controlled to enable tissue ingrowth and inhibit wound contraction. The dermal portion serves as a template for the infiltration of fibroblasts, macrophages, lymphocytes and endothelial cells that form a neovascular network. As healing progresses, native collagen is deposited by fibroblasts, and the collagen portion of INTEGRA template is biodegraded over approximately 30 days. Upon adequate vascularization of the dermal layer and availability of donor autograft tissue, the temporary 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 confluent stratum corneum, thereby closing the wound reconstituting a functional dermis and epidermis.

IV. Contraindications

Use of INTEGRA template is contraindicated in those patients with known hypersensitivity to bovine collagen or chondroitin materials.

INTEGRA template should not be used on clinically diagnosed infected wounds.

V. Warnings and Precautions

Refer to device labeling for a list of the warnings and precautions.

VI. Alternative Practices and Procedures

Alternative treatments for scar contracture release include the use of full- or split-thickness autograft or skin flaps when sufficient donor sites are available. Tissue Expanders are also used in an attempt to increase the amount of skin available for autografting. In all cases, the use of autograft creates a donor wound site.

VII. Adverse Effects

Reconstructive Surgery Study and Retrospective Contracture Reconstruction Survey

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.

Table 1: 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 was no mortality reported in either the Reconstructive Surgery Study or the Retrospective Contracture Reconstruction Survey. There were no reports of infection in the Reconstructive Surgery Study. In the Retrospective Contracture Reconstruction Survey the overall infection rate reported for INTEGRA template-treated wound sites was 20.5% (26 of 127 sites). The consequence of infection at Integra treated sites included partial and complete INTEGRA template graft loss.

Information about the adverse events observed in the treatment of patients with life threatening thermal injuries can be found in the summary of safety and effectiveness document (SSED) for P900033 and in device labeling which is attached.

VIII. Marketing History

FDA approved the original PMA for INTEGRA® Dermal Regeneration Template for the burn indication on March 1, 1996.

INTEGRA® Dermal Regeneration Template is approved for marketing for burns and reconstructive surgery in the European Union, Argentina, Australia, Brazil, Canada, Chile, China, Dominican Republic, El Salvador, Hong Kong, Korea, Mexico, New Zealand, Panama, Singapore, Taiwan, Thailand and Uruguay.

The device has not been recalled or withdrawn for any reason related to the safety or effectiveness of the device.

IX. Summary of Preclinical Studies

The testing performed in the original application was adequate to support the safety and effectiveness of the device for the treatment of patients with life-threatening thermal injuries. A summary of this testing can be found in the SSED for P900033.

X. Clinical Study and Survey for Contracture Reconstruction

The clinical data provided in the original application were sufficient to provide a reasonable assurance of safety and effectiveness for the treatment of patients with life-threatening thermal injuries.

The following is a summary of the clinical data to support approval for the indication of contracture reconstruction.

A. Reconstructive Surgery Study

Study Design and Methods - This study was a prospective, non-randomized assessment of the use of INTEGRA® Dermal Regeneration Template for the reconstructive surgery of scars and contractures. Scars were excised and INTEGRA template was applied to excised wound sites. Following formation of the neodermis, the INTEGRA template silicone layer was removed and a thin epidermal autograft applied. A 4-mm punch biopsy was performed weekly on the first 10 patients in the series prior to removal of the INTEGRA template silicone layer. A 4-mm punch biopsy was performed on all patients before removal of the silicone layer and at monthly intervals for as long as two years. Biopsy specimens were preserved, paraffin sections prepared, and evaluated.

Study Endpoints - Postoperative function and cosmesis were compared with the pre-operative status. An independent review panel assessed the patients using a modified Vancouver Burn Scar Assessment Scale. Pigmentation, vascularity, pliability and scar heights were assessed independently, with increasing score being assigned to a greater pathological condition. A score of 0 is normal (i.e., no scar) and score of 15 represents the worst scar.

Patients or their parents assessed treatment outcomes 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. Parameters evaluated included range of motion, softness, appearance, pruritus and dryness of the scar.

Results - A series of 20 consecutive patients with 30 scar contracture sites were surgically treated to reconstruct the skin following acute burn surgery. The most common reasons for surgery were scar contracture release (19) and painful scars (6). The other reasons were resurfacing of scars (5), tight scars (4) and donor site (1).

Independent assessment using the modified Vancouver Burn Scar Assessment Scale showed an average improvement from a total score of 13.3 preoperatively to a score of 9.0 post-operatively.

For the patient satisfaction assessments, patients/parents reported mean scores of 72% for range of movement, 62% for softness, 59% for appearance, 27% for pruritis and 14% for dryness.

Results-Histopathology - Serial histologic microscopic examinations were performed on preserved (10% formalin and paraffin wax) and stained (hematoxylin and eosin) wound biopsies from patients treated with INTEGRA Dermal Regeneration Template. These observations revealed, in general, four phases of integration. The earliest phase is characterized by the accumulation of wound fluid and adherence of the matrix to the wound. This is followed by the second phase, which is characterized by the accumulation of myofibroblasts in the dermal matrix. The third phase is characterized by the migration of endothelial cells and the establishment of new blood vessels. The fourth phase starts when the matrix has been populated with fibroblasts and new collagen gradually replaces the bovine collagen of the Dermal Regeneration Template. The observed histologic phases seen with INTEGRA Dermal Regeneration Template are similar to wound-healing phases and skin graft "take" seen with standard skin grafting.

B. Retrospective Contracture Reconstruction Survey

These data were collected in a retrospective convenience survey of surgeons known to use INTEGRA® Dermal Regeneration Template for reconstructive surgery. Information was received from 13 of 19 physicians surveyed who reported on 89 patients and 127 anatomic sites. The demographic profile for the reported patients was: mean age 24.8, age range <1 to 72, gender 52 males and 37 females. Surgeons were requested to report on all treated patients regardless of outcome. However, it is not known whether the surgeons reported on all the patients receiving INTEGRA for contracture reconstruction in their practices. The surgeons or their staff completed case report forms reporting their experiences, including patient safety information. Available data were abstracted from the patients' medical records.

Data were reported for eighty-nine patients with 127 contracture revision sites who were treated with INTEGRA template. All the treated patients for whom data were reported were trauma victims with permanent impairments, disabilities and disfigurements from their original injuries. The most common etiology was a thermal injury; 112 sites (88.8%). Reconstruction occurred from a few months up to 20 years

after the initial injury. Children made up 47.2% of the population, 20.2% of the patients were 10 years old or less and 27.0% were between 11 and 20 years old.

The anatomical sites requiring reconstruction varied among the patients included in the survey. The most common sites were head and neck 32 sites (25.2%), upper extremities - 20 sites (15.7%), hand – 17 sites (13.4%), lower extremities – 17 sites (13.4%), and Axilla – 15 sites (11.8%). Other sites included: Chest (7.1%), groin/genitalia (4.7%), abdomen (3.1%), back (1.6%) and other (0.8%).

Safety information obtained from this survey is reported in Table 1.

XI. Conclusions

The data presented in this PMA supplement, coupled with the extensive safety and effectiveness data and reports of clinical experience available on INTEGRA dermal regeneration template for a similar indication, provide reasonable assurance of the safety and effectiveness of this device. The INTEGRA Dermal Regeneration Template provides a reasonable, alternative method for reconstructing contractures that have failed standard therapy or are associated with physical or logistical factors that preclude the use of a routine graft and/or flap procedure.

XII. Gender Bias

No selection bias because of gender was identified during the review of the submission and no significant gender differences were noted in the clinical studies. The ratio of male to female patient enrollment in the studies is reflective of the type and frequency of the wounds and their underlying distribution in the general population.

XIII. Panel Recommendations

Pursuant to section 515 (c) (2) of the Food, Drug and Cosmetic Act (the Act) as amended by the Safe Medical Devices Act of 1990 this PMA supplement was not referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation. This is because the information in this PMA supplement substantially duplicates information previously reviewed by this panel.

XIV. CDRH Decision

Based upon a review of the data contained in this panel track supplement, CDRH determined that the INTEGRA dermal regeneration template has been shown to be safe and effective for the indication specified in this labeling.

FDA issued an approval order on April 19, 2002

XV. Approval Specifications

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, Adverse Reactions in the labeling.

Postapproval Requirement and Restrictions: See the approval order.