BIOENGINEERED SKIN SUBSTITUTES

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INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee's specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

This document addresses the use of human skin substitutes (also referred to as artificial skin) for the treatment of acute and chronic non-healing wounds and soft tissue grafting. The goals are to provide temporary wound coverage, provide complete wound closure, reduce time to healing, lessen pain, minimize postoperative contracture, improve aesthetics and functional abilities, obviate the need for more extensive treatments such as skin grafting or amputation, and improve overall quality of life.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

REASONABLE AND MEDICALLY NECESSARY:

**AlloDerm®** is considered MEDICALLY NECESSARY in post-mastectomy breast reconstructive surgery for at least one of the following indications:
- When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; OR
- When there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; OR
- The infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

**Apligraf®** is considered MEDICALLY NECESSARY for at least one of the following indications:
- Venous insufficiency skin ulcers with all the following characteristics:
  - Chronic, non-infected, partial or full-thickness ulcers due to venous insufficiency,
  - Standard therapeutic compression also in use,
  - At least one month of conventional ulcer therapy (such as standard dressing changes, and standard therapeutic compression) has been ineffective.
- Diabetic foot ulcers with all the following characteristics:
  - Full-thickness neuropathic diabetic foot ulcers,
  - Extends through the dermis but without tendon, muscle, joint capsule, or bone exposure,
  - At least four weeks of conventional ulcer therapy (such as surgical debridement, complete off-loading and standard dressing changes) has been ineffective.

**Artiss®** fibrin sealant is considered MEDICALLY NECESSARY for the treatment of individuals with severe burns when all of the following criteria are met:
- The treatment is specific to noninfected partial-thickness burn wounds and donor site wounds,
- Excision of the burn wound is complete (e.g., nonviable tissue are removed) and homeostasis achieved,
- Sufficient autograft tissue is not available at the time of excision, OR
- Autograft is not desirable due to the individual's physiologic condition (e.g., individual has multisystem injuries such that creating new wounds may cause undue stress).

**Biobrane®** is considered MEDICALLY NECESSARY for the treatment of burn wounds when all of the following criteria are met:
- The treatment is specific to noninfected partial-thickness burn wounds and donor site wounds,
- Excision of the burn wound is complete (e.g., nonviable tissue are removed) and homeostasis achieved,
- Sufficient autograft tissue is not available at the time of excision, OR
- Autograft is not desirable due to the individual's physiologic condition (e.g., individual has multisystem injuries such that creating new wounds may cause undue stress).

**Dermagraft®** is considered **MEDICALLY NECESSARY** when used for at least one of the following indications:
- The treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that has not adequately responded to standard therapy, that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure; OR
- When used on wounds with dystrophic epidermolysis bullosa.

**Epicel™** is considered **MEDICALLY NECESSARY** for the treatment of at least one of the following indications:
- The treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that has not adequately responded to standard therapy, that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure; OR
- When used on wounds with dystrophic epidermolysis bullosa.

**Epicel™** is considered **MEDICALLY NECESSARY** when used for at least one of the following indications:
- The burns comprise 30 percent or greater of total body surface area,
- When used in conjunction with split-thickness autografts or alone in individuals for whom split-thickness autografts may not be an option due to the severity and extent of their burns,
- Approval has been obtained for the use of Epicel™ in accordance with the above US Food and Drug Administration (FDA)-labeled indications under the Humanitarian Device Exemption (HDE).

**Epifix®** is considered **MEDICALLY NECESSARY** for the treatment of:
- Neuropathic diabetic foot ulcers (DFUs) when all of the following criteria are met:
  - The patient has the current medical diagnosis of either Type I or Type II diabetes mellitus
  - The patient does not have a current HbA1c reading above 12%
  - Only for partial or full thickness ulcers of greater than four weeks in duration, with documented failure of prior treatment to heal the wound
  - Ulcer extends through the dermis, with or without tendon, muscle, capsule or bone exposure
  - Ulcer must exhibit no signs of infection
  - Patient must have adequate circulation to the affected extremity
  - Conservative measures must be in place (e.g., debridement, non-weight bearing, use of pressure-reducing footwear)
- Non-infected partial or full-thickness skin ulcers due to venous insufficiency (e.g., venous stasis ulcers):
  - Only for ulcers that have failed to respond to documented conservative measures of greater than four (4) weeks in duration (e.g., wound tissue hydration with saline, regular dressing changes, debridement, and standard therapeutic compression).

**Grafix®Core** is considered **MEDICALLY NECESSARY** for the treatment of Standard diabetic foot ulcers (DFUs) when all of the following criteria are met:
- The patient has the current medical diagnosis of either Type I or Type II diabetes mellitus,
- The patient does not have a current HbA1c reading above 12%,
- Only for partial or full thickness ulcers of greater than four weeks in duration, with documented failure of prior treatment to heal the wound,
- Ulcer extends through the dermis, with or without tendon, muscle, capsule or bone exposure,
- Ulcer must exhibit no signs of infection,
- Patient must have adequate circulation to the affected extremity,
- Conservative measures must be in place:
  - Debridement of necrotic tissue
Non-weight bearing regimen
Use of pressure-reducing footwear

**GRAFTJACKET® Regenerative Tissue Matrix** is considered **MEDICALLY NECESSARY** for treatment of full-thickness diabetic foot ulcers greater than four-week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.

**Hyalomatrix®** is considered **MEDICALLY NECESSARY** for the treatment of deep burns and full-thickness wounds; also provides a wound preparation support for the implantation of autologous skin grafts.

**Integra™ Bilayer Matrix Wound Dressing, Dermal Regeneration Template, and Meshed Bilayer Wound Matrix**, artificial skin substitutes products, are considered **MEDICALLY NECESSARY** in the post-excisional treatment of severe burns (full-thickness, 3rd degree), or (deep partial-thickness, 2nd degree) when autografting is not feasible due to the individual’s weakened physiological condition where there is a limited amount of their own skin to use or they are too ill to have more wound sites created.

**Oasis® Wound Matrix and Oasis® Ultra Tri-Layer Matrix** are considered **MEDICALLY NECESSARY** for treatment of chronic, noninfected, partial- or full-thickness lower-extremity vascular ulcers, which have not adequately responded following a one-month period of conventional ulcer therapy.

**OrCel™**, a composite skin substitute, is considered **MEDICALLY NECESSARY** for the following indications:
- Dystrophic epidermolysis bullosa in children who are undergoing reconstructive hand surgery.
- Full-thickness (3rd degree) and partial-thickness (2nd degree) thermal burns.
- Healing donor site wounds in burn victims.

**Primatrix™, Dermal Repair Scaffold** is an acellular dermal tissue matrix considered **MEDICALLY NECESSARY** for wound management for the following conditions:
- Partial thickness wounds
- Full thickness wounds with or without exposed bone and/or exposed tendon
- Pressure ulcers
- Diabetic ulcers
- Venous ulcers
- Surgical wounds
- Trauma wounds
- Tunneled/undermined wounds
- Draining wounds

Treatment courses typically involve a maximum of five applications.

**TransCyte™**, a allogeneic human dermal fibroblasts dressing, is considered **MEDICALLY NECESSARY** for the following uses:
- Temporary wound covering to treat surgically excised full-thickness (3rd degree) and deep partial-thickness (2nd degree) thermal burn wounds in persons who require such a covering before autograft placement.
- The treatment of middermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting.

**Theraskin®, a biologically active cryopreserved human skin allograft**, is considered **MEDICALLY NECESSARY**
for the treatment of venous stasis ulcers (VSUs) and standard diabetic foot ulcers (DFUs) when all of the following criteria are met:

- The patient has the current medical diagnosis of either Type I or Type II diabetes mellitus,
- The patient does not have a current HbA1c reading above 12%,
- Only for partial or full thickness ulcers of greater than four weeks in duration, with documented failure of prior treatment to heal the wound,
- Ulcer extends through the dermis, with or without tendon, muscle, capsule or bone exposure,
- Ulcer must exhibit no signs of infection,
- Patient must have adequate circulation to the affected extremity,
- Conservative measures must be in place:
  - Debridement of necrotic tissue
  - Non-weight bearing regimen
  - Use of pressure-reducing footwear
  - Acceptable methods of wound care, such as saline moistened dressings

**INVESTIGATIONAL AND NOT MEDICALLY NECESSARY:**

- When criteria above are not met, or for any other application not listed, the use of AlloDerm®, Apligraf®, Artiss®, Biobrane®, Dermagraft®, Epigel®, Epifix®, Grafix®, Hyalomatrix®, GRAFTJACKET® Regenerative Tissue Matrix, Integra Bilayer Matrix Wound Dressing®, Oasis®, OrCel®, Primatrix™, TransCyte®, and Theraskin® are considered EXPERIMENTAL/INVESTIGATIONAL AND NOT MEDICALLY NECESSARY.

- The use of all other allogeneic, xenographic, synthetic and composite skin substitutes products for wound healing or soft tissue grafting, not addressed in the Coverage Determination section, including but not limited to the following products, is considered INVESTIGATIONAL AND NOT MEDICALLY NECESSARY:
  - AlloMax™
  - Allopatch HD™
  - Alloskin™
  - Alloskin RT™
  - AmnioFix™
  - Arthroflex™
  - Avaulta Plus™
  - C-QUR™
  - CellerateRX®
  - CollaFix™
  - Collamend™
  - Conexa™
  - CorMatrix®
  - CRXa™
  - Cuffpatch™
  - Cymetra®
  - Dermacell™
  - Dermamatrix™
  - Endoform™
- ENDURAgen™
- Epidex®
- E-Z Derm™
- Flex HD®
- Gammagraft™
- GORE BIO-A® Fistula Plug
- Graftjacket™ Xpress injectable
- Hyalomatrix®
- Inforce®
- Integra™ Neural Wrap
- Matriderm®
- Matristem®
- MediHoney®
- Medeor™
- Mediskin®
- Memoderm™
- Menaflex™ Collagen Meniscus Implant
- Meso BioMatrix™
- Neoform Dermis™
- Neuragen®
- NeuraWrap™
- Neuroflex™
- NeuroMatrix™
- OrthADAPT™
- Pelvicol®
- Pelvisoft®
- Permacol™
- PTFE felt™
- Promogran™
- Puracol®
- SportMesh™
- Strattice™
- SurgiMend®
- Surgisis® Biodesign™AFP™ Anal Fistula Plug
- Surgisis® Biodesign™ Gold™ Inguinal Hernia Matrix
- Surgisis® Biodesign™ Recto-Vaginal Fistula Plug
- Talymed™
- TenoGlide™
- TissueMend®
- Unite™
- Veritas® Collagen Matrix
- Xelma™
- X-Repair™
- XenMatrix™
Clinical Considerations:

General Utilization Guidelines:

- Treatment with skin substitute occurs weekly, and is expected to last up to twelve (12) weeks.
- Reapplication of skin substitute within one week for the same ulcer is considered not reasonable and necessary.
- Re-treatment within one year following the last successful application with is considered not reasonable and necessary.
- Re-treatment of an ulcer following the unsuccessful treatment where it consisted of two (2) failed applications is considered not reasonable and necessary.

Contraindications include:

- Evidence of arterial occlusive disease, i.e., ankle-brachial index (ABI) < 0.65.
- Evidence of infection in ulcer(s) targeted for treatment.
- Exudate consistent with heavy bacterial contamination, or necrotic tissue that would interfere with graft take and healing.
- Active Charcot disease.
- Hypersensitivity or allergy to any components of the skin substitutes

The efficacy and safety of these skin substitutes in patients who are pregnant or lactating, have uncontrolled diabetes, or are currently being treated with corticosteroids, immunosuppressants, or chemotherapy have not been established (Sabolinski et al., 1996; Falanga et al., 1998; Falanga and Sabolinski, 1999).

Evaluation/Risk Assessment/Screening

- Initial and continuous pressure ulcer risk assessment using reliable scales
- Nutritional assessment with a validated measure
- Document medical and surgical history
- Assessment of psychosocial conditions and quality of life
- Environmental assessment
- Physical examination, including wound assessment
- Diagnostic tests

Prevention/Rehabilitation

- Skin inspection and maintenance
- Hydration and nutrition plan of care
- Rehabilitative and restorative programs
- Positioning standards of care to manage pressure ulcers
- Off-loading equipment including chairs, intensive care, and operating rooms
- Interdisciplinary team approach
- Education

Management/Treatment

- Remove/alleviate all causes of pressure ulcer damage
- Debride, cleanse, and dress the wound
- Advanced or adjuvant interventions
- Surgical interventions
Follow-Up Care
The individual should be self-sufficient with follow-up care or have the required support system to participate in the follow-up care associated with skin substitutes.

BACKGROUND:
Skin wounds can be caused by a variety of different events, including thermal burns, venous stasis, ischemia, pressure, trauma, or surgery, and as a result of an underlying skin disorder such as epidermolysis bullosa (EB). According to the American Burn Association (ABA), an estimated 1 million burn injuries occur annually in the United States. Burn injuries result in approximately 4500 deaths, 45,000 hospitalizations, and 700,000 emergency room visits per year. The average size of a burn injury among patients admitted to burn centers is approximately 14% of the total body surface area (TBSA). Partial-thickness, or second-degree, burns are those in which there is damage to the epidermis and the upper portion of the dermis. Serious burns are treated by split-thickness autographs (STGs), which include part of the dermis, and are obtained from such areas as the inner thigh or buttocks, and placed on the wound.

Chronic wounds, including venous ulcers, diabetic foot ulcers, and pressure sores, are a major public health problem in the United States; the total prevalence of these wounds has been estimated to range from 3 to 6 million. Difficult-to-heal wounds lead to high rates of morbidity and mortality, negative effects on quality of life, and high healthcare costs. Lower extremity ulcers affect approximately 1% of the adult population and approximately 3.6% of persons older than 65 years. While lower extremity ulcers have numerous causes, such as venous disease, arterial disease, mixed venous-arterial disease, diabetic neuropathy, trauma, immobility, and vasculitis, over 90% of the lesions are related to venous or arterial disease and neuropathy.

SKIN GRAFTING.
There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products may be derived from allogeneic, xenographic, synthetic, or a combination of any or all of these types of materials.

Autologous skin grafts also referred to as autografts, are permanent covers that use skin from different parts of the individual's body. These grafts consist of the epidermis and a dermal component of variable thickness. A split-thickness skin graft (STSG) includes the entire epidermis and a portion of the dermis. A full-thickness skin graft (FTSG) removes all the layers of the skin. Although autologous skin grafts are the optimum choice for wound coverage, areas of skin for harvesting may be limited, particularly in cases of large burns; in addition, the procedures are invasive and painful. Allografts (which use skin from another human [e.g., cadaver]) and xenografts (which use skin from another species [e.g., porcine or bovine]) may also be employed as temporary skin replacements, but they must later be covered by an autograft.

BIOENGINEERED SKIN SUBSTITUTES.
Because of problems inherent with autografts, allografts, and xenografts, bioengineered skin substitutes have been developed. These are products used for non-healing wound treatment and soft tissue grafting on patients with life threatening full-thickness (3rd degree) or deep partial-thickness (2nd degree) burns, surgical wounds, diabetic ulcers, venous ulcers, and epidermolysis bullosa. These products are...
manufactured by starting with a few human cells in which tissue engineers simulate the environments that allow cells to develop into viable tissue. The specific procedure varies by company, but it generally involves seeding the selected cells onto some type of matrix, where they are then provided with the proteins and growth factors necessary for them to grow and multiply into the desired tissue.

A variety of biosynthetic and tissue-engineered human skin equivalents (HSE) are manufactured under an array of trade names and marketed for various purposes. All of these products are procured, produced, manufactured or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products.

Bioengineered skin substitutes are classified into the following types:

- Cultured epithelial autografts
- Human skin allografts derived from donated human cadaver tissue
- Allogenic matrices derived from human neonatal fibroblasts
- Composite matrices derived from human keratinocytes, fibroblasts, and bovine or porcine collagen
- Acellular matrices derived from porcine or bovine collagen

CULTURED EPITHELIAL AUTOGRRAFTS (CEAs): Examples include, but may not be limited to:

- **Epicel™** (cultured epidermal autograft [CEA]) (Genzyme Tissue Repair; Cambridge, MA). Sheets of skin cells intended to replace the epidermis on severely burned patients. The patient’s own skin cells are grown or cultured from a postage-stamp sized sample of the patient’s own healthy skin. The skin cells are grown on a layer of irradiated mouse cells, making Epicel® a xenotransplantation product. (Genzyme Corp., 2007).

- **EpiDex™** (DFH Pharmaceuticals, Inc.; Fort Worth, TX) is a fully differentiated autologous epidermal equivalent derived from outer root sheath keratinocytes that is grown directly from plucked hair follicles. Cell cultures expand for five to six weeks, after which time the product is applied nonsurgically. One study was insufficiently powered to allow assumptions about its effect on the population. In a second study, there was no significant difference between the groups in the frequency of complete ulcer closure or time to complete closure. At this time, EpiDex™ has no FDA designation.

- **Epifix®.** A natural, amniotic membrane allograft used in the treatment of chronic and acute wounds and is considered reasonable and necessary in the wound management for patients with neuropathic diabetic foot ulcers (DFUs) and non-infected partial and full-thickness skin ulcers due to venous insufficiency.

- **Grafix Core®** (cellular repair matrix) HCT/P is a cryopreserved chorion matrix and GRAFIX PRIME is a cryopreserved amnion matrix retaining the neonatal mesenchymal stem cells, fibroblasts and epithelial cells that are known to produce biologically active growth factors in the native tissue. These growth factors provide the product with multipotent characteristics, meaning that it can support migration, proliferation and differentiation of several types of host cells (epithelial, endothelial, fibroblasts) known to support tissue regeneration.

- **Hyalomatrix™** (Laserskin®) (Fidia Advanced Biopolymers; Abano Terme, Italy). A bioresorbable dermal substitute made of HYAFF®, a long-acting derivative of hyaluronic acid providing a microenvironment purportedly suitable for optimal tissue repair and accelerated wound healing. Specifically intended for the treatment of deep burns and full-thickness wounds; also provides a wound preparation support for the implantation of autologous skin grafts.
HUMAN SKIN ALLOGRAFTS DERIVED FROM DONATED HUMAN CADAVER TISSUE: Examples include, but may not be limited to:

- **AlloDerm®** (Life Cell Corp.; The Woodlands, TX). AlloDerm is an acellular dermal matrix designed to serve as a biologic scaffold for normal tissue remodeling. Processed from human cadaver skin with the cells responsible for immune response and graft rejection removed. The remainder is a matrix or framework of natural biological components, ready to enable the body to mount its own tissue regeneration process. (Jones et al., 2002).

- **Alloskin™** (AlloSource Inc.; Centennial, CO). An allograft derived from epidermal and dermal cadaveric tissue and suggested for wound care.

- **Cymetra®** (Life Cell Corp.; The Woodlands, TX). An injectable form of AlloDerm® that has been processed into micronized particles; suggested for the correction of soft-tissue defects, such as injection laryngoplasty.

- **GammaGraft™** (Promethean LifeSciences, Inc.; Pittsburgh, PA). GammaGraft™ is an irradiated composite allograft that can be stored at room temperature. According to the manufacturer, GammaGraft™ is indicated in various types of wounds and is used primarily as a temporary dressing that may require multiple applications.

- **GRAFTJACKET® Regenerative Tissue Matrix** (Wright Medical Technology; Arlington, TN). This is a product derived from cadaver skin from which the epidermis and all cellular components are removed while preserving the matrix and biochemical factors. Graftjacket is to be used for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument (Wright Medical Technology Inc., 2008). It is suggested for diabetic foot ulcers.

- **GRAFTJACKET® EXPRESS Scaffold** (Wright Medical Technology; Arlington, TN). This allograft is a micronized (finely ground) decellularized soft tissue scaffold indicated for the repair or replacement of damaged or inadequate integumental tissue, specifically deep, dermal wounds that exhibit tunneling and extension from the wound base that may move into the tendon and bone.

- **TheraSkin®** (Soluble Solutions, Newport News, Va.). A biologically active cryopreserved human skin allograft with both epidermis and dermis layers; the cellular and extracellular composition provides a supply of growth factors, cytokines and collagen to supposedly promote wound healing.

ALLOGENIC MATRICES DERIVED FROM HUMAN NEONATAL FIBROBLASTS: Examples include, but may not be limited to:

- **AlloMax™** (Bard Davol, Inc.). A sterile regenerative human collagen matrix suggested for soft tissue repair, including hernia and abdominal wall reconstruction, and post-mastectomy breast reconstruction.

- **Celaderm®** (Advanced BioHealing; Westport, CT) is a cultured epithelial allograft that contains metabolically active human foreskin-derived allogeneic keratinocytes. At this time, this product has no FDA designation.

- **Dermagraft®** (Advanced BioHealing; Westport, CT / Smith & Nephew, Inc.; La Jolla, CA). This product is a living dermal replacement that employs human neonatal foreskin fibroblasts. The mesh is a biodegradable material that disappears after being in place for three to four weeks. It is used in the treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that extends through the dermis, but without tendon, muscle, joint capsule, or bone exposure. It is also used for treatment of wounds in individuals with dystrophic epidermolysis bullosa (DEB).
COMPOSITE MATRICES DERIVED FROM HUMAN KERATINOCYTES, FIBROBLASTS AND BOVINE OR PORCINE COLLAGEN: Examples include, but may not be limited to:

- **Apligraf®** (Organogenesis, Inc.; Canton, MA). Formerly marketed as Graftskin. Much like human skin as it has two primary layers: the epidermal (outer) layer consists of live keratinocytes, while the dermal (inner) layer contains living fibroblasts. Also referred to as human skin equivalent.

- **OrCel™** (formally Composite Cultured Skin) (Ortec International, Inc.; New York, NY). A bi-layered skin substitute that uses human epidermal keratinocytes and dermal fibroblasts that are cultured into two separate layers on a bovine collagen sponge. As healing occurs at the site of the wound, the OrCel® dissolves and the patient’s own skin cells then replace the OrCel® cells to create a new skin surface.

- **TransCyte™** (formally Dermagraft TC™ [Dermagraft Transitional Covering]) (Advanced BioHealing; Westport, CT). A human fibroblast-derived temporary skin substitute consisting of a polymer membrane and neonatal human fibroblast cells cultured under aseptic conditions in vitro on a nylon mesh. Purportedly, as fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors.

ACELLULAR MATRICES DERIVED FROM PORCINE, OVINE, OR BOVINE COLLAGEN: Examples include, but may not be limited to:

- **Biobrane®** (UDL Laboratories Inc.; Rockford, IL) (formerly a product of Mylan/Bertek Laboratories). This product is an acellular dermal matrix constructed using collagen (porcine type 1) that is incorporated with both silicone and nylon, and mechanically bonded to a flexible knitted nylon fabric. The semipermeable membrane is comparable to human skin as it controls the loss of water vapor, allows for drainage of exudates, and provides permeability to topical antibiotics. The nylon/silicone membrane provides a flexible adherent covering for the wound surface.

- **Endoform™** Dermal Template (Mesynthes Ltd, Wellington, New Zealand). This product is an extracellular matrix derived from sheep collagen (forestomach) and intended for single use in the treatment of wounds.

- **EZ Derm™** (Brennen Medical, Inc.; St. Paul, MN). A porcine derived xenograft in which the collagen has been chemically cross-linked with aldehyde (a chemical compound) purportedly to provide strength and durability.

- **Integra® Dermal Regeneration Template** (Integra LifeSciences Corp.; Plainsboro, NJ) is a bi-layered extracellular matrix of fibers of cross-linked bovine collagen and chondroitin-6-sulfate (a component of cartilage) with silicone backing. Once an organized regeneration of dermal tissue is formed (neodermis), the disposable silicone sheet is removed and an ultrathin autograft is placed over the neodermis.

- **Integra™ Bilayer Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). A biodegradable porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan intended to provide a scaffold for cellular invasion and capillary growth. Wound closure is typically complete within 30 days.

- **Integra™ Flowable Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ) is comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan, which is hydrated with saline for injection into difficult to access wound sites and tunneled wounds.
Matristem® Wound Matrix (ACell Inc. Jessup, MD) is a porcine-derived, single or multi-layer, extracellular matrix sheet. This product is used for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh’s surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second degree burns, skin tears), and draining wounds.

Matristem Micromatrix® (ACell Powder Wound Dressing) (ACell Inc. Jessup, MD) is composed of porcine collagen from urinary bladder matrix that is lyophilized to be used as a topical application. This product is marketed as a wound healing powder that helps regenerate hair in the donor and recipient regions of hair transplant individuals.

Matristem® Burn Matrix (ACell Inc. Jessup, MD) is a porcine-derived, single or multi-layer, extracellular matrix sheet.

Oasis Wound Matrix™ (Cook Biotech, Inc; West Lafayette, IN). A naturally derived ECM, created from the submucosal layer of porcine small intestine; proposed to support the body's healing process by providing an acellular scaffold that accommodates remodeling of host tissue. This product also contains other biologically active components that may stimulate healing such as glycosaminoglycans, proteoglycans, fibronectin, and growth factors (Mostow et al., 2005).

Oasis Burn Matrix™ (Cook Biotech, Inc; West Lafayette, IN) is a product derived from porcine small intestinal submucosa (SIS). This product is intended for the management of second degree burns and donor sites.

PriMatrix™ Dermal Repair Scaffold (TEI Biosciences Inc.; Boston, MA) (formerly DressSkin). A naturally derived, ECM created from the submucosal layer of porcine small intestine; proposed to support the body's healing process by providing an acellular scaffold that accommodates remodeling of host tissue. Primatrix is designed to incorporate collagen into the wound bed and stimulate rapid tissue granulation and native collagen production. A viral inactivation process is included in its manufacture to protect against potentially contaminating viruses. This biological matrix is appropriate for treatment of a variety of different types of wounds, including skin ulcers, second-degree burns, surgical wounds, trauma wounds, post-Mohs surgical wounds, and tunneled wounds (TEI Biosciences, 2008).

REGULATORY STATUS:

1. U.S. FOOD AND DRUG ADMINISTRATION (FDA):

   Depending on the purpose of the product and how it functions, skin substitutes are regulated by the FDA premarket approval (PMA) process, 510(k) premarket notification process, or the FDA regulations for banked human tissue.

   Products that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA process as a class III, high-risk device and require clinical data to support their claims for use. These devices may be used as a long-term skin substitute or a temporary synthetic skin substitute. They actively promote healing by interacting directly or indirectly with the body tissues. Examples of these devices include Apligraf® (Organogenesis Inc., Canton, MA) and Dermagraft® (Advanced BioHealing, Inc., LaJolla, CA).

   Other wound care devices (Class II) are approved by the 510(k) process, and their primary purpose is to
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protect the wound and provide a scaffold for healing. They may or may not be integrated into the body tissue. Some devices are rejected by the body after approximately ten days to several weeks and removed prior to definitive wound therapy or skin grafting. Integra™ Bilayer Matrix Wound Dressing (BMWD) (Integra LifeSciences Corp., Plainsboro, NJ) and Oasis® Wound Matrix (Cook Biotech, Inc., West Lafayette, IN) are examples of these devices.

Human tissue products (acellular) require no FDA clearance or approval and are intended for homologous use only. [Title 21 Code of Federal Regulations (CFR), Section 1271.10(a) 2005].

National Government Services does not cover Class II or Human Tissue products unless otherwise specified in an attached article or a separate LCD.

National Government Services will consider the use of Class III products eligible for coverage when used in keeping with the FDA's approved indications for those products.

Donated skin that requires minimal processing and is not significantly changed in structure from its natural form is classified by the FDA as banked human tissue. It is not considered a medical device, and does not require PMA or 510(k) approval. Donated skin is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue. AATB oversees a voluntary accreditation program and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Tissue establishments must register with the FDA and list each cell or tissue produced. An example of a banked human tissue product is AlloDerm, an acellular dermal matrix (FDA, 2004; Department of Health and Human Services, 2001).

- **AlloDerm®** (Life Cell Corp.; The Woodlands, TX). AlloDerm® is regulated as human tissue and subject to the rules and regulations of banked human tissue, regulated by the American Association of Tissue Banks (AATB); hence, it is not subject to FDA pre-notification approval (LifeCELL Corporation, 2008).

- **Alloskin™** (AlloSource Inc.; Centennial, CO). FDA regulation of human tissue does not include review and approval for safety and effectiveness.

- **Apligraf®** (Organogenesis, Inc.; Canton, MA). Apligraf gained FDA PMA based on its efficacy with venous ulcers. Apligraf® also has FDA PMA for use in the treatment of diabetic foot ulcers.

- **Biobrane®** (UDL Laboratories Inc.; Rockford, IL). This product holds an FDA 510(k) approval for the treatment of clean partial-thickness burn wounds and donor site wounds.

- **Celaderm®** (Advanced BioHealing; Westport, CT). At this time, this product has no FDA designation, and no published study outcomes were found in the literature. Individuals are currently being enrolled in an FDA-approved study to evaluate the safety of Celaderm® in humans and to assess its potential for acceleration of healing of venous leg ulcers.

- **Cymetra®** (Life Cell Corp.; The Woodlands, TX). The FDA considers Cymetra® banked human tissue because it is minimally processed and not significantly changed in its structure from the natural material.

- **Dermagraft®** (Advanced BioHealing; Westport, CT / Smith & Nephew, Inc.; La Jolla, CA). Dermagraft® has received FDA premarket approval (PMA) for use in the treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure.

- **Endoform™** Dermal Template (Mesynthes Ltd, Wellington, New Zealand). Endoform™ received an
FDA 510(k) Premarket Notification from the FDA. The product is similar to Integra™ and Oasis,™ which were cited as predicate devices. Indications are similar to other acellular matrix products and include the following: treatment of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence, trauma wounds (e.g., abrasions, lacerations, second-degree burns, and skin tears), and draining wounds.

- **Epice™** (Genzyme Tissue Repair; Cambridge, MA). The FDA considers Epice™ to be a cultured epidermal autograft, dressing, wound, and burn interactive that does not require an FDA designation. For burns, Epice™ has been approved by the FDA under the humanitarian device (HDE) designation for use in individuals who have deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30 percent.

- **EpiDex™** (DFH Pharmaceuticals, Inc.; Fort Worth, TX). At this time, EpiDex™ has no FDA designation.

- **EpiFix®** (MiMedx Group, Inc.). Epifix® is regulated by the FDA as Human Cells, Tissues, and Cellular and Tissue Based Products. Indications include wound management for patients with neuropathic diabetic foot ulcers (DFUs) and non-infected partial and full-thickness skin ulcers due to venous insufficiency (e.g., venous stasis ulcers).

- **EZ Derm™** (Brennen Medical, Inc.; St. Paul, MN). EZ Derm™ has FDA 510(k) approval for the treatment of partial-thickness burns and venous, diabetic, and pressure ulcers.

- **GammaGraft™** (Promethean LifeSciences, Inc.; Pittsburgh, PA). At this time, it has No FDA designation.

- **Grafix Core (Osiris Therapeutics, Inc.).**

- **Graftjacket®**: Graftjacket Matrix, Graftjacket Xpress Scaffold, and Graftjacket Ulcer Repair Matrix (Wright Medical Technology; Arlington, TN): These products are made from human donor skin, which undergoes a process that removes the epidermis and dermal cells, thereby creating an acellular dermis. Similar to AlloDerm, human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient are regulated as human cell, tissue, and cellular- and tissue-based products; hence, it is not subjected to FDA pre-notification approval (FDA, 2009).

- **Hyalomatrix®** (Laserskin®) (Fidia Advanced Biopolymers; Abano Terme, Italy). This product has received FDA 510(k) approval and is indicated for the management of wounds in the granulation phase (e.g., pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second-degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, and wounds and burns treated with meshed grafts).

- **Integra® Dermal Regeneration Template** (Integra LifeSciences Corp.; Plainsboro, NJ). Integra® has an FDA PMA for 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 physiologic condition of the individual. This product also has an FDA PMA for repair of scar contractures.

- **Integra™ Bilayer Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). FDA has approved these products for indications that include management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers,
chronic vascular ulcers, surgical wound (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, and skin tears), and draining wounds.

- **Integra™ Flowable Wound Matrix** (Integra LifeSciences Corp.; Plainsboro, NJ). According to the FDA 510(k) summary, this product is equivalent in function and intended use to the Integra™ Matrix Wound Dressing.

- **Matristem Micromatrix®** (ACell Inc. Jessup, MD). Matristem Micromatrix® has also received 510k Premarket Notification for the same indications as Matristem® Wound Matrix. This product is marketed as a wound healing powder that helps regenerate hair in the donor and recipient regions of hair transplant individuals.

- **Matristem® Wound Matrix** (ACell Inc. Jessup, MD). Matristem® Wound Matrix has received FDA Premarket Notification for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh’s surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second degree burns, skin tears), and draining wounds.

- **Oasis® Wound Matrix**: Oasis Wound Matrix is regulated by the FDA as a Class II (moderate risk) device. This product received FDA 510(k) approval (K061711), granted to Cook Biotech Inc. on July 19, 2006. It is an animal-derived extracellular matrix that is supplied sterile and is intended for single use in the management of various wounds such as partial and full-thickness wounds, pressure, venous, diabetic, and chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds (FDA 2006b). The product is identical to an earlier product developed by Cook Biotech Inc. (SIS wound dressing II, K993948, issued January 6, 2000) (FDA, 2000). The FDA approved a name change to Oasis Wound Matrix to acknowledge that it contains glycosaminoglycans and other matrix components not found in other purified collagen-alone materials that can stimulate cell differentiation in cell culture assay, an indicator of bioactivity (Schaum and Farley, 2006).

- **OrCel™** (Ortec International, Inc.; New York, NY). OrCel™ has received FDA PMA for the treatment of fresh, clean split-thickness donor site wounds. OrCel™ has received an HDE for the treatment of surgical wounds and donor sites associated with mitten-hand deformities in individuals who have recessive dystrophic epidermolysis bullosa (RDEB).

- **PriMatrix™ Dermal Repair Scaffold** (TEI Biosciences Inc.; Boston, MA) (formerly DressSkin). This product received initial FDA 510(k) approval (K061407), granted to TEI Biosciences Inc. on June 29, 2006. This product is indicated for the management of wounds, including partial- and full-thickness wounds, pressure, diabetic, and venous ulcers, second-degree burns, surgical wounds, trauma wounds, tunneled/undermined wounds, and draining wounds (FDA, 2006a).

- **Promogran®**: Promogran Matrix Wound Dressing received FDA 510(k) approval (K014129), granted to Johnson & Johnson Medical Ltd. on February 14, 2002. Promogran is indicated for use in patients with diabetic ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, full- and partial-thickness wounds, donor sites and other bleeding surfaces, abrasions, traumatic wounds, and dehisced surgical wounds (FDA, 2002).

- **TheraSkin®** (Soluble Solutions, Newport News, Va.) is a biologically active cryopreserved human skin allograft and has both epidermis and dermis layers. The FDA has classified TheraSkin™ as banked human tissue and, therefore, is subject to the rules and regulations of banked human tissue.
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- **TransCyte™** (Advanced BioHealing; Westport, CT). TransCyte™ received FDA PMA as a temporary wound covering for surgically excised full-thickness and deep partial-thickness burn wounds in individuals who require such a covering prior to autograft placement.

- **Xelma®**: Xelma has not yet received premarket approval from the FDA.

### 2. CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):

**Local Coverage Determination (LCD):**

- (L26003) Biologic Products for Wound Treatment and Surgical Interventions
- A50627 - AlloDerm® Regenerative Tissue Matrix – Related to LCD L26003
- A46092 - Apligraf® – Related to LCD L26003
- A45056 - Biologic Products for Wound Treatment and Surgical Interventions - Supplemental Instructions Article
- A46090 - Dermagraft® – Related to LCD L26003
- A52159 - EpiFix® - Related to LCD L26003
- A53933 - Grafix® - Related to LCD L26003
- A49404 - GRAFTJACKET® Regenerative Tissue Matrix-Ulcer Repair and GRAFTJACKET® XPRESS Flowable Soft Tissue Scaffold – Related to LCD L26003
- A46085 - Integra® Dermal Regeneration Template and Integra® Bilayer Matrix Wound Dressing – Related to LCD L26003
- A46082 - OASIS® Wound Matrix and OASIS® Ultra Tri-Layer Matrix – Related to LCD L26003
- A52087 - Primatrix™ Dermal Repair Scaffold - Related to LCD L26003
- A50504 - TheraSkin® – Related to LCD L26003
- A40531 - Skin substitutes

CMS covers the use of skin substitutes and related products in the treatment of lower extremity ulcer disease. The LCD does not pertain or otherwise apply to the use of any skin substitutes or related products in the treatment of burns, skin cancer, or for true reconstructive surgery.

The Food and Drug Administration (FDA) distinguishes between products according to function (wound management, e.g., wound dressings and wound treatment, e.g., bioactive skin substitutes.) The former (Class II) requires 510(k) pre-market notification for FDA clearance while the latter (Class III) requires pre-market approval.

Human tissue products (acellular) require no FDA clearance or approval and are intended for homologous use only. [Title 21 Code of Federal Regulations (CFR), Section 1271.10(a) 2005]

National Government Services does not cover Class II or Human Tissue products unless otherwise specified in an attached article or a separate LCD.

National Government Services will consider the use of Class III products eligible for coverage when used in keeping with the FDA’s approved indications for those products.

**Indications:**

The following general indications and limitations to Medicare coverage and payment apply to all materials and services related to skin substitute / replacement.

Applied to wounds that have demonstrated a failed or insufficient response to no fewer than four
weeks of conservative wound care measures. For initial applications of skin substitutes/replacements, a failed response to conservative measures is defined as an ulcer that has increased in size or depth or for which there has been less than 30% closure from baseline. For the purposes of this LCD, a chronic cutaneous ulcer is defined as a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure. A burn wound is defined as a cutaneous wound induced by thermal, chemical, or electrical injury. An acute wound is of recent occurrence and usually traumatic in nature.

Managed wounds should be clean and free of infection and are of reasonable size (at least 1.0 cm² and with adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination (presence of acceptable peripheral pulses and/or Doppler toe signals and/or ABI of no less than 0.65).

Management of chronic wounds should include treating the underlying condition and co-morbidities, which might include optimizing blood glucose control in patients with diabetic ulcers, ensuring adequate nutrition status in debilitated patients, revascularization in patients with ischemic artery disease, and pain management.

In addition to the type of dressing used in treating chronic wounds, several common principles apply to the management of most chronic wounds:

a. Removal of dead and devitalized tissue which provides a nidus for bacterial infection (not colonization),
b. Aggressive antibiotic treatment of peri-wound and wound infections,
c. Mechanical measures which may favorably alter local hemodynamics or ameliorate adverse physical forces, (most common are offloading and debridement for diabetic ulcers and compression for venous ulcers) and
d. Optimization of general nutrition.

Application of Bioengineered Skin Substitutes will be covered when the following conditions are met and documented as appropriate for the individual patient:

1. Presence of neuropathic diabetic foot ulcers for greater than four (4) weeks’ duration.
2. Presence of venous stasis ulcers of greater than three (3) months’ duration that have failed to respond to documented conservative measures for greater than two (2) months’ duration.
3. Presence of neuropathic diabetic foot ulcers that have failed to respond to documented conservative measures for greater than one (1) month’s duration. These measures must include appropriate steps to off-load pressure during treatment.
4. Presence of partial or full-thickness ulcers.
5. Measurements of the initial ulcer size, the size following cessation of any conservative management and the size at the beginning of skin substitute treatment.
6. In all cases, the ulcer must be free of infection and underlying osteomyelitis. Documentation must be provided that these conditions have been successfully treated and resolved prior to instituting skin substitute treatment.

Documentation Requirements:

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.
1. The medical record must document that wound treatments with skin substitutes/replacements are accompanied by appropriate wound dressing changes during the healing period and by appropriate compressive dressings during follow-up, including, for neuropathic diabetic foot ulcers, appropriate steps to off-load wound pressure during the follow-up.

2. The medical record documentation must clearly document the medical necessity and performance of the extent of site preparation procedures billed.

3. Rationale for the selection of a biological product for surgical interventions in repair of anatomic defects or reconstruction work must be documented in the medical record and submitted to Medicare upon request.

3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):
Minnesota DHS has guidance regarding specialized wound treatment technology and specifically addresses platelet rich plasma systems (e.g., AutoloGel, Magellan); negative pressure wound therapy devices, and Electro-magnetic/ultrasound therapy. DHS does not address Bioengineered Skin Substitutes in its Provider Manual or other specific provider references.

Criteria for Specialized Wound Treatment for Chronic Wounds
Authorization for specialized wound therapy for chronic wounds will be considered when a wound does not respond to standard wound treatment for at least a 30 day period. For all wounds, documentation and a comprehensive treatment plan, before requesting authorization for a specialized wound therapy product, is required and includes the following:

- Wound type, including:
  - Etiology and stage when appropriate
  - Date of onset
  - Evaluation
  - Previous wound care and assessments done by a licensed medical professional

- Weekly wound measurements to assess the appropriateness of current wound treatment. If no improvement to the wound, the wound treatment must be changed. This must be done by nursing staff in the skilled facility or by a licensed medical professional in the home setting.

- Application of dressings to maintain a continuously moist wound environment must have been tried prior to requesting a specialized wound therapy product (gel dressings).

- Impregnated dressings have been tried when applicable (e.g., sodium, antimicrobial, collagen petroleum).

- Debridement of necrotic tissue - mechanical, surgical/chemical.

- Evaluation and provision for adequate nutritional status. Include both prealbumin and albumin levels. Ideally, albumin levels are 3.5 – 5. If albumin levels are below 3.5, specialized wound therapy may be approved if prealbumin levels are 20-40, show improvement over the previous 30 days and if there is a nutritional plan in place written by an appropriate professional. Specialized wound therapy will not be authorized for albumin levels below 2.8. Baseline albumin and prealbumin levels are required and as medically necessary thereafter. If albumin levels are below 3.5, enteral nutritional support may be covered. Refer to Enteral Nutritional Products policy.

- Moisture and incontinence have been addressed and appropriately managed.

- Compliance issues are addressed (i.e., missed medical appointments, refusing dressing changes, repositioning, smoking, poor nutritional intake or choices).
• Medical intervention/correction of underlying conditions that may hinder the healing process of the wound (i.e., local or distant infections are addressed).
• Assessment of medications that may delay healing (e.g., systemic steroids, immunosuppressive drugs).
• Evaluation of arterial sufficiency when appropriate.
• Licensed professional (RN, LPN, PT) services in place for treatment in the home.
• Document how this request is appropriate for the type of wound being treated.

**CLINICAL EVIDENCE:**

**SUMMARY:**
There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products may be derived from allogeneic, xenographic, synthetic, or a combination of any or all of these types of materials. All of these products are procured, produced, manufactured or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products. Therefore, each product must be reviewed and judged on the basis of the available scientific evidence specific to that product. Unfortunately, the majority of these products have no peer-reviewed, published studies available to assist in the evaluation of their safety and efficacy. In such circumstances, products are considered investigational and not medically necessary based on a lack of data addressing both the safety and efficacy of the product in question. For other products, there may be one or more published studies of varying quality.

The overall body of published evidence regarding the safety and efficacy of biological tissue-engineered skin substitutes is limited, and at the present time does not clearly demonstrate a benefit of these products compared with optimal standard wound care. None of the available studies provided an adequate direct comparison of the different biological tissue-engineered skin substitute products. Additional research, including well-designed randomized controlled or comparative studies, is needed to establish the safety, efficacy, and comparative effectiveness of the different skin substitute products and to define appropriate patient selection criteria.

**GROUPS POLICY:**

**American Diabetes Association (ADA):** The ADA published the findings of a consensus conference held in April 1999 on the care of diabetic foot wounds. The statement contained a section on the evaluation of new treatments (ADA, 1999). The following conclusions were reached:
• Any new device, dressing, or biological or pharmacological agent should be evaluated in a consistent and rigorous manner and should not be adopted without substantial evidence of its efficacy. New technologies include Apligraf, growth factors, electrical stimulation, cold laser, and heat.
• The reference standard for evaluation of new treatments is the randomized controlled trial, which should consist of a sufficient number of patients to obtain adequate statistical power.
• The relevant outcomes, wound healing and the rate of healing, depend upon ulcer severity and the treatment regimen as well as variables such as patient compliance.
• Patient inclusion and exclusion criteria must be described, including key wound parameters (e.g.,
area and depth), ulcer duration, and presence of infection, neuropathy, and/or ischemia.

- All patients in controlled trials must receive standardized wound care, including off-loading, a defined debridement protocol, and evaluation of patient compliance with the protocol.
- Primary study endpoints should include the proportion of patients with complete wound healing, as defined by the Wound Healing Society, within a specific time frame. Secondary endpoints include time to healing, velocity of wound healing, rate of recurrence, quality of life, and cost-effectiveness.

Wound Healing Society (WHS): An advisory panel convened by the WHS published guidelines for the treatment of arterial insufficiency ulcers in 2006. This panel concluded that "extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required." The WHS guideline also stated that "despite the existence of animal studies, case series, and a small number of RCTs to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers, there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made" (Hopf et al., 2006). A second advisory panel published guidelines for the treatment of acute wounds. The panel concluded that when an excised burn with a total burn surface area (TBSA) is so large that donor sites for split-thickness skin grafts are not enough, permanent skin substitutes can be used as skin replacement with no fear of rejection. In addition, the third panel advised that nonimmunogenic skin substitutes might also serve as permanent skin replacement with no fear of rejection. Temporary biologic, synthetic, biosynthetic, or bioengineered dressings are not sufficient to provide permanent burn wound closure, but they can allow for the wound to be free of infection until the permanent wound heals completely (Franz et al., 2008). In a set of guidelines published in 2006 for the treatment of chronic wounds, an advisory panel concluded that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (e.g., growth factors) for healing of venous ulcers (Robson et al., 2006).

Association for the Advancement of Wound Care (AAWC): In 2005, the AAWC presented a summary algorithm for venous ulcer care that recommends use of dressings that maintain a moist environment. If no healing is seen in 30 days, the algorithm recommends biologic dressings, including matrix dressings (AAWC, 2005).

American College of Foot and Ankle Surgeons (ACFAS): In a clinical practice guideline on diabetic foot disorders, the ACFAS makes general references to active or interactive dressings. This guideline concludes that "although these products are commonly used in clinical practice, they have not yet been conclusively shown to expedite wound healing" (Frykberg, 2002).

American Podiatric Medical Association (APMA): The APMA includes Oasis Wound Matrix in its list of therapeutic products that have been evaluated and granted the APMA "seal of approval" (APMA, 2009).

American Society of Plastic Surgeons (ASPS): The ASPS clinical practice guidelines for management of chronic lower extremity wounds advise that appropriate dressings be used to maintain a moist environment, and state that the available evidence does not support the superiority of any particular dressing material. The guideline mentions that bioactive dressings, including topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor, are all products that can be considered (ASPS, 2007).

Wound, Ostomy and Continence Nurses Society (WOCN): The WOCN has released a set of guidelines
for the management of wounds and use of Oasis Wound Matrix product (WOCN, 2006).

**APPLICABLE CODES:**

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

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<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C9354</td>
<td>Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm</td>
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<td>C9358</td>
<td>Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm</td>
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<td>Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm</td>
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<td>Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm</td>
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<td>Epifix, per sq cm</td>
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<td>Skin substitute, Endoform Dermal Template, per sq cm</td>
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<td>Surgical preparation codes for skin replacement surgery</td>
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<td>15272</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)</td>
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<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children</td>
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<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15276</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15277</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children</td>
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<td>15278</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15777</td>
<td>Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (e.g., breast, trunk) (List separately in addition to code for primary procedure)</td>
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REFERENCES:


15. Association for the Advancement of Wound Care (AAWC) venous ulcer guideline references. Malvern (PA): Association for the Advancement of Wound Care (AAWC); 2010 Dec. 14 p. Electronic copies: Available in Portable.
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47. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994;271(1):59-63.


66. Landsman A, Cook J, Cook E, et al. A retrospective clinical study of 214 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin) on the treatment of diabetic Foot ulcers and venous leg ulcers. Foot & Ankle Specialist. Accepted for publication.


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POLICY HISTORY:

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<td>03/28/2013</td>
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<tr>
<td>11/15/2013</td>
<td>Published to UCare.org</td>
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<tr>
<td>07/01/2015</td>
<td>Policy Update:</td>
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<tr>
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<td>• Added applicable ICD-10 codes to the Coding Section. The list of codes may not be</td>
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<td>all-inclusive and does not denote coverage.</td>
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<td>• Policy identification number updated to 2015M0011A.</td>
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<td>• Approved by the Medical Policy Committee (MPC).</td>
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<td>• Changed some products from investigative to medically necessary and proven</td>
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<td>• Added products</td>
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<td>• Policy identification number updated to 2015M0011B.</td>
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