Subject: Skin Substitutes for Chronic Wound Healing in the Out-Patient Setting		Original Effective Date: 4/23/20
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Contents

DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina clinical policy document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [4]

Normal healthy skin provides a protective barrier against microbes, water loss, and ultraviolet light damage; helps with thermoregulation; and provides tactile sensations. Wounds are disruptions of the skin's structural and functional integrity and normally transition through distinct phases until the skin's structure and function are restored. Chronic wounds have failed to pass through the normal healing process. A wound may be considered chronic if it has not entered the cellular migration and proliferation phase after 4 weeks (30 days) of standard treatment. The usual treatment or standard of care for established chronic wounds incorporates common principles that apply to managing all wound types:

- Remove necrotic tissue through debridement (typically sharp debridement).
- Maintain moisture balance by selecting the proper wound dressing to control exudate.
- Take measures to prevent or treat wound infections.
- Correct ischemia in the wound area.
- For venous leg ulcers, apply some form of compression.
- For diabetic foot ulcers, apply some form of offloading.

However, the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies. Using saline wet-to-dry gauze on any chronic wound is no longer considered part of standard wound care. Patients with chronic wounds, such as diabetic foot ulcers and venous leg ulcers, experience loss of function, pain, wound recurrence, and significant morbidity. Usual care for chronic wounds involves removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. If these procedures fail to restore the healing process, additional therapies such as the application of skin substitutes to promote wound healing may be considered. The three most common uses for skin substitutes are for the treatment of venous leg ulcers, diabetic foot ulcers and burns.

Skin substitutes are proposed as a treatment to cover open chronic ulcers and promote wound healing, with the goals of preventing infection and amputation. They are thought to function by physically covering the wound and providing extracellular matrices to induce regeneration and immune function. Skin substitutes, also known as bioengineered, tissue-engineered, or artificial skin, are a heterogeneous group of products and can generally be classified into 3 main types: cellular (comprised of living cells), acellular (composed of synthetic materials or tissue from which living cells have been removed), or a combination of cellular and acellular components. Skin Substitutes are also categorized as tissue-engineered products that that may be biological (i.e., using human cells, animal cells, or both, in a scaffold of natural or synthetic extracellular matrices) or biosynthetic (i.e., with both biological and synthetic elements comprising the scaffold or matrix). There is no universally accepted classification system that allows for simple categorization of all the products that are commercially available. Each skin substitute has unique advantages and disadvantages. The type of skin substitute chosen depends upon the type of wound (ie, acute, chronic), its etiology (eg, trauma, chronic inflammation), the skin component that requires replacement (ie, epidermis, dermis, or both), and need for permanence. Regardless of the source or classification, the skin substitute provides a matrix into which cells can migrate. Cells are placed in single or bilayer matrixes. Skin substitutes are developed from different materials and therefore are evaluated by different regulatory pathways as outlined below:

Food and Drug Administration (FDA): The term "skin substitutes" describes a heterogeneous collection of products, materials, and applications intended to heal open wounds; the various types are regulated differently.

- Premarket Approval (PMA): Devices that support or sustain human life or have the potential to cause risk of illness or injury are approved through the PMA process. Examples of products approved through the PMA process include (Apligraf [P950032A] and, Dermagraft [P000036A]) under product code MGR (dressing, wound and burn, interactive). For information on additional products, search by product code or applicant name in the Premarket Approval Database.[2]
- Premarket Clearance (510(k)): Devices that are deemed substantively equivalent to legally marketed predicate devices that do not require a PMA can be marketed under this designation. Examples of products reviewed in this evidence base had 510(k) clearance under product code KGN (dressing, wound, collagen) include (Oasis [K061711]), and clearance under product code FRO (dressing, wound, drug) (Talymed [K102002]). For information on additional products, search by product code or applicant name in the 510(k) Premarket Notification Database.[2]
- Public Health Service (PHS) 361 [21 Code of Federal Regulations (CFR) 1270 & 1271]: Human cells, tissues, and cellular and tissue-based products (HCT/Ps) can only be commercially prepared by licensed establishments (FDA). Examples of products include (TheraSkin; LifeNet Health). Search by establishment name or other information in the Human Cell and Tissue Establishment Registration database. [2]

At the time this MCP was developed and according to various databases there is an exhaustive list of skin substitute products and some are regulated by FDA and sold in the United States through the premarket approval (PMA) process, the 510(k) premarket submission process, or are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps) derived from human cadaver skin and human placental membranes.[3] Any list of commercially available skin substitutes should not be considered comprehensive because the industry is expanding with ongoing FDA approvals, including skin substitute products currently in development or in the clinical trial phase. A technology assessment report from the Agency for Healthcare Research and Quality (AHRQ) from February, 2020 listed 76 products classified as skin substitutes.[4]

Definitions

Acellular Products:

Dermal substitutes made from natural biological materials includes decellularized human cadaver dermis, human amniotic membranes, and animal tissue. These are the most common commercially available skin substitute products for the treatment or management of chronic wounds.

Cellular Products:

Autograft: A sample of the patient's own healthy skin is harvested and placed in the ulcer in split- or full-thickness from pinch or mesh grafts or patients' cells may be grown in a laboratory to form a thin film (cultured keratinocyte autograft, or cultured epidermal autograft), which can take 3 to 4 weeks; their downside is the potential for donor site morbidity.

Allografts: Skin or tissue is harvested from another human such as a cadaver or from cultured keratinocytes or cultured epidermal fibroblasts.

Xenograft: Skin or tissue is harvested from an animal with similar skin structure (usually pigs or cows).

*Note: This policy does not address Cellular products.

Bioengineered are skin substitutes that may be completely synthetic (e.g., polymer matrix) or may be composite products (biosynthetic, i.e., contain 2 or more components, which may be biological or synthetic)

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/Ps): Products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

POSITION STATEMENT CRITERIA [1 2 4 50-52]

Note: There may be state mandates and health plan regulations regarding coverage of skin substitutes therefore please check mandates and individual state health plan regulations before applying this MCP. Mandates and/or regulations supersede this MCP. Breast Reconstruction is NOT addressed in this MCP as there are Federal/State mandates that are applicable.

For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed **prior to** applying the criteria set forth in this clinical policy. Medicare Part B accepts the U.S. Food and Drug Administration classification and description of any skin substitute. The U.S. Food and Drug Administration has regulated most skin substitutes as medical devices. However, some are regulated as human tissue and are, therefore, subject to the rules and regulations of banked human tissue, not the U.S. Food and Drug Administration approval process (L35041; National Coverage Determination 270.5). Refer to the CMS website at http://www.cms.gov for additional information. [1]

- ❑ Medicare [1] considers skin substitutes to be reasonable and medically necessary for treatment of ulcers or wounds with failed response that are (L35041):
  - Partial- or full-thickness ulcers, not involving tendon, muscle, or joint capsule or exhibiting exposed bone or sinus tracts, with a clean granular base.
  - Skin deficit at least 1 cm^2 in size.
  - Clean and free of necrotic debris or exudate.
  - Have adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination (e.g., Ankle-Brachial Index of no less than 0.60, toe pressure greater than 30 mmHg).
  - For diabetic foot ulcers, the member's medical record reflects a diagnosis of type 1 or type 2 diabetes and also reflects medical management for this condition.

- ❑ Medicare [1] considers application of a skin substitute graft for lower extremity chronic wound (diabetic foot ulcer or venous leg ulcer) to be reasonable and necessary when the following conditions are met for the individual member (L35041):

- Presence of neuropathic diabetic foot ulcer(s) having failed to respond to documented conservative wound-care measures of greater than four weeks, during which the member is compliant with recommendations, and without evidence of underlying osteomyelitis or nidus of infection.
- Presence of a venous stasis ulcer for at least three months but unresponsive to appropriate wound care for at least 30 days with documented compliance.
- Presence of a full-thickness skin loss ulcer that is the result of abscess, injury, or trauma that has failed to respond to appropriate control of infection, foreign body, tumor resection, or other disease process for a period of four weeks or longer.

For Medicaid/Market Place members, when state coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid/Market Place manual for any coverage provisions pertaining to this clinical policy.

Clinical Criteria:

Before medical necessity criteria can be applied ALL of the following product specific regulations and standards must be met:

- ❑ The skin substitute product must meet ALL applicable state and federal regulations; and
- ❑ The skin substitute product must meet ALL applicable regulations and standards established by the American Association of Tissue Banks for procuring and processing human cells, tissues, and cellular or tissue-based products (HCT/Ps); OR
- ❑ The skin substitute product must meet ALL product-specific FDA requirements that include one of the following: [ONE]
  - The product has received FDA premarket approval for the requested indication; or
  - The product has received FDA 510K premarket clearance for the requested indication

AND MUST BE ONE OF THE FOLLOWING:

- ❑ Skin substitutes that may be considered medically necessary for **WOUND HEALING** [e.g.; burns, diabetic foot ulcers, venous leg ulcers, venous stasis ulcers] includes but is not limited to the following: [ALL]
  - **Allopatch** [Musculoskeletal Transplant Foundation, Edison, NJ]: acellular human dermis derived from human allograft skin used for the treatment of partial and full-thickness neuropathic diabetic foot ulcers and venous ulcers.
  - **AmnioBand AmnioBand Membrane or Guardian** (Musculoskeletal Transplant Foundation, Edison, NJ): allograft made of human amnion and chorion used for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

- **Apligraf (e.g. Graftskin)** [Organogenesis Inc., Canton, Massachusetts]: culture-derived human skin equivalent (HSE) used to treat noninfected, partial and full-thickness skin ulcers due to venous insufficiency and for full-thickness neuropathic diabetic foot ulcers nonresponsive to standard wound therapydiabetic foot ulcers and venous stasis leg ulcers.
- **Artiss** [Baxter Healthcare Corporation, Deerfield, IL]**:** a slow-setting fibrin sealant consisting of human fibrinogen and low concentration human thrombin used for burns
- **Biobrane** [UDL Laboratories Inc., Rockford, Illinois]**:** biosynthetic dressing used for a temporary covering of partial-thickness, freshly debrided or excised burn wounds in the absence of coagulum, eschare and necrotic tissue.
- **DermaCELL, Dermacell AWM, Dermacell Porous** [(LifeNet Health®, Virginia Beach, VA]: acellular human dermis allograft collagen scaffold used for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
- **Dermagraft** [Organogenesis Inc., Canton, Massachusetts]**:** human fibroblast-derived dermal substitute used to treat lower extremity full-thickness diabetic foot ulcers on the fore foot, toes or heal, of longer than six weeks' duration, that extend through the dermis, and are refractory to standard wound care management.
- **Epicel** [Genzyme Biosurgery, Cambridge, MA]: cultured epidermal autograft used for deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30 %. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option.
- **EpiFix** [Mimedx Group Inc., Marietta, Georgia]: a multi-layer biologic dehydrated human amniotic membrane allograft used for acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness wounds; venous, diabetic, pressure, and chronic vascular ulcers; trauma wounds, including burns; and surgical wounds.
- **Grafix Cellular Repair Matrix (Grafix Core, Grafix PL Core, Grafix Prime and Grafix PL Prime)** [Osiris Therapeutics, Inc., Columbia, MD]: cryopreserved, human placental, extracellular matrix treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
- **Graftjacket Regenerative Tissue Matrix** [Wright Medical Technology, Inc., Arlington, TN]: acellular human dermal collagen template used for treatment of full-thickness diabetic foot ulcers greater than 6-weeks duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.
- **Integra Bilayer Matrix Wound Dressing** [Lifesciences Corporation, Plainsboro, New Jersey]**:** collagen-glycosaminoglycan copolymers used for the treatment of severe burns, and partial and full-thickness neuropathic diabetic foot ulcers and venous ulcers.
- **Integra Dermal Regeneration Template** [Lifesciences Corporation, Plainsboro, New Jersey] **:** collagen-glycosaminoglycan copolymers used for the treatment of severe burns and partial and full-thickness neuropathic diabetic foot ulcers.
- **Integra Matrix** [Lifesciences Corporation, Plainsboro, New Jersey]: collagen-glycosaminoglycan copolymers used for the treatment of severe burns.

- **OASIS Burn Matrix** [Cook Biotech Inc., West Lafayette, Indiana]: extracellular matrix created from the submucosal layer of porcine small intestine used for burns
- **OASIS Wound Matrix & OASIS Ultra Tri-Layer Matrix** [Cook Biotech Inc., West Lafayette, Indiana]: naturally derived, extracellular matrix (ECM) created from the submucosal layer of porcine small intestine. Oasis is an established treatment option for partial or full-thickness diabetic foot ulcers of greater than four weeks duration. Oasis may also be used to treat venous stasis ulcers of one month duration that do not respond to standard wound care. The Oasis Ultra Tri-Layer Matrix incorporates three layers of the same structural components as the single layer matrix and is used in the treatment of larger wounds.
- **OrCel** [Ortec International Inc., New York, New York]: bilayered cellular matrix used for healing donor site wounds in burns.
- **Suprathel® Suprathel®** [PolyMedics Innovations GmbH, Denkendorf, Germany]: synthetic epithelial substitute used for the treatment of first- and second-degree burns.
- **TheraSkin** [LifeNet Health, Inc., Virginia Beach, VA]: human skin allograft with epidermis and dermis layers used to treat partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed and partial or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed.
- **TransCyte** [Shire Regenerative Medicine, San Diego, California]: human fibroblast-derived temporary wound cover used for full-thickness and deep partial-thickness thermal burns. It is used as a temporary wound covering until autograft is possible.

❑ **AND Must meet the below specific criteria:**

1. Skin substitutes are **medically necessary** for diabetic foot ulcers, venous stasis ulcers, or venous leg ulcers when all of the following criteria are met: [ALL]
   - Age ≥ 18 years, or type 1 diabetic;
   - Wound is chronic, defined as a wound that does not respond to at least 4 weeks of standard wound treatment as a component of organized, comprehensive conservative therapy;
   - Standard wound care has failed, evidenced by all of the following:
     - The ulcer or skin deficit has been treated with appropriate wound-care measures, including debridement, standard dressings (including silver dressings), compression, off-loading; and
     - Wound has increased in size or depth; or has not changed in baseline size or depth and there is no indication that improvement is likely (such as granulation, epithelialization or progress towards closing);
   - Nicotine use adversely affects healing. Documentation is required of effort to cease nicotine use, including from sources other than cigarettes but excluding nicotine replacement therapy, for at

least 4 weeks during conservative wound care and prior to planned bioengineered skin replacement therapy, or no nicotine use;

- Wound characteristics and treatment plan are documented including all of the following:
  - Partial- or full-thickness skin defect, clean and free of necrotic debris, exudate, or infection;
  - Tissue approximation would cause excessive tension or functional loss;
  - No involvement of tendon, muscle, joint capsule, or exposed bone or sinus tracts;
  - No wound infection; wound must be clean and free of necrotic debris or exudate;

AND the following wound specific criteria must be met:

2. For lower extremity chronic wounds (diabetic foot ulcer or venous leg ulcer), one of the following:
   - **Diabetic foot ulcer** (DFU) at least 1 cm^2 in size., and all of the following: [ALL]
     - Hgb AIc of ≤ 8 or documentation of improving control; and
     - Documented conservative wound care for ≥ than 4 weeks; and
     - Wound is without evidence of osteomyelitis or nidus of infection; and
     - Adequate circulation in affected extremity by physical examination or imaging (e.g., palpable dorsalis pedis or posterior tibial artery pulse or an ankle brachial index ≥ 0.60); and
     - Under current diabetes medical management including nutritional support and treatment history with attention to certain comorbidities (e.g., vascular disease, neuropathy, osteomyelitis) with evidence of stable glycated hemoglobin levels; and
     - Applied in conjunction with conservative therapy (e.g., moist wound environment with dressings or non-weight bearing or pressure reduction interventions).

   - **Venous stasis ulcer or venous leg ulcers** (VSU or VLU), at least 1 cm^2 in size and all of the following: [ALL]
     - A chronic, non-infected ulcer VSU or VLU has failed to respond to documented conservative wound-care measures for ≥ 4 weeks with documented compliance; and
     - Adequate circulation in affected extremity by physical examination or imaging (e.g., palpable dorsalis pedis or posterior tibial artery pulse or an ankle brachial index ≥ 0.60); and

- Under current medical management for venous insufficiency, with objective documentation that supports the diagnosis. Member must have an assessment of history (e.g., prior ulcers, thrombosis risks), physical exam (e.g., edema, skin changes); and
- Applied in conjunction with conservative therapy (e.g., compression wraps).

3. Skin substitutes are **medically necessary** for partial- or full-thickness thermal burn wounds when all of the following criteria are met: [ALL]
   - Sufficient full-thickness autograft is not available at the time of excision or is not feasible due to the physiological condition of the patient; and
   - No evidence of burn wound infection; and
   - Excision of the burn wound is complete (e.g., nonviable tissue is removed) and homeostasis is achieved.

CONTRAINDICATIONS [2 54 55]

Contraindications for the use of skin substitutes include all of the following: [ALL]

- Active Charcot arthropathy of the ulcer surface; and
- Continued tobacco smoking; and
- Evidence of active infection or vasculitis in ulcer(s) targeted for treatment; and
- Exudate consistent with heavy bacterial contamination, or eschar or necrotic tissue that would interfere with graft take and healing; and
- Hypersensitivity or allergy to any components of the skin substitute (e.g., allergy to avian, bovine, porcine, equine products); and
- Inadequate control of underlying conditions or exacerbating factors (e.g., uncontrolled diabetes with Hgb A1c > 8%, or no documented improvement of glucose levels in the last 4 weeks; and
- Skin grafting or replacement for partial thickness loss with the retention of epithelial appendages, as epithelium will repopulate the deficit from the appendages, contraindicating the benefit of over-grafting.

CONTINUATION OF THERAPY [2]

All of the following guidelines for treatment apply:

- ❑ Continued treatment of chronic wounds will last no more than 12 weeks; and
- ❑ All skin substitute applications must comply with FDA guidelines for the specific product, not to exceed 10 applications or treatments per 12 week period of care; and

- ❑ Only one skin substitute will be simultaneously in place per wound episode. Product change within the wound episode is allowed, not to exceed the 10 application limit per wound per 12 week period of care; and
- ❑ Repeat or alternative applications of skin substitute grafts when a previous full course of applications was unsuccessful. Unsuccessful treatment is defined as increase in size or depth of an ulcer or no change in baseline size or depth, and no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress toward closing) for a period of four weeks after the start of therapy; and
- ❑ Re-treatment of healed ulcers, those showing greater than 75 percent size reduction, and those smaller than 0.5 cm2; and
- ❑ Re-treatment within one year of any given course of skin substitute treatment for a venous stasis ulcer or diabetic foot ulcer because re-treatment is considered treatment failure.

LIMITATIONS [2]

- ❑ Skin substitutes are **not medically necessary** for the following: [ALL]
  - Any indications not noted in the clinical criteria section above; and
  - Decubitus ulcer treatment; and
  - Continued treatment when the ulcer fails to heal by ≥ 50% within the first 6 weeks of treatment; and
  - Treatment beyond 12 weeks is considered not medically necessary regardless of wound status; and
  - Continued skin substitute use after treatment failure, which is defined as the repeat or alternative application course (of up to 12 weeks) of skin substitute grafts within one year of any given course of skin substitute treatment for a venous stasis ulcer or diabetic foot ulcer; and
  - Retreatment of healed ulcers (those showing greater than 75% size reduction and smaller than 1 square cm).

- ❑ All other skin substitute products used for wound healing not outlined in the clinical criteria section above are considered **experimental, investigational and unproven** due to insufficient evidence in the peer reviewed medical literature. Products include but are not limited to all the following: [ALL]
  - AlloDerm;
  - AlloSkin or AlloSkin RT;
  - AltiPly;

- AmnioAMP-MP;
- Amnioarmor;
- AmnioCore;
- AmnioCyte Plus;
- AMNIOEXCEL (including AMNIOEXCEL Amniotic Allograft Membrane);
- AmnioHeal Plus;
- AMNIOMATRIX;
- Amnio-Maxx or Amnio-Maxx;
- AMNIOREPAIR;
- AmnioText or AmnioText patch;
- Amnio Wound;
- Amniply;
- Artacent (including Artacent Flex and Artacent Wound);
- Arthroflex;
- Biobrane (except for indication specified in this policy);
- BioNextPATCH;
- carePATCH;
- Cellesta products (e.g., Cellesta Amniotic Membrane, Cellesta Flowable Amnion);
- Clarix Regenerative Matrix;
- Cogenex Amniotic Membrane or Cogenex Flowable Amnion;
- Coll-e-Derm;
- CoreCyte;
- CoreText;
- Corplex or Corplex P;
- Cryo-Cord;
- Cymetra;
- CYGNUS (including CYGNUS MATRIX, CYGNUS MAX, and CYGNUS SOLO);
- Cytal (including Cytal Wound Matrix, MatriStem Wound Matrix, and Multilayer Wound Matrix);
- Dermacyte Anmniotic Membrane Allograft or Dermacyte Amniotic Wound Care Liquid;
- Derma-Gide
- Derm-Maxx;
- EpiCord (including EpiCord Dehydrated Human Umbilical Cord Allograft);
- E-Z Derm;
- FlexHD or Allopatch;
- GammaGraft;
- Genesis Amniotic Membrane;
- hMatrix;
- Hyalomatrix
- Integra Flowable Wound Matrix;
- Interfyl;
- Kerecis Omega3;
- Keroxx (including Keroxx Flowable Wound Matrix);

- Marigen Omega3;
- Matrion;
- MatriStem (including MatriStem Burn Matrix, MatriStem Micromatrix, and MatriStem Wound Matrix);
- Mediskin;
- Memoderm;
- MIRODERM Biologic Wound Matrix;
- NEOPATCH;
- NEOX Wound Allograft;
- Novachor;
- Novafix DL;
- NuDyn;
- OrCel (except for indication specified in this policy);
- PalinGen (including PalinGen Membrane, PalinGen XPlus Membrane, PalinGen XPlus Hydromembrane, PalinGen Flow, PalinGen SportFlow, and ProMatrX ACF);
- PriMatrix;
- Procenta;
- ProText;
- PuraPly (including PuraPly Antimicrobial Wound Matrix, PuraPly AM, PuraPly AM XT, PuraPly XT);
- REGUaRD;
- Restorigin;
- Revita;
- SkinTE;
- Strattice;
- Stravix;
- SurFactor;
- surgiGRAFT;
- SurgiMend;
- Talymed;
- TissueMend;
- Transcyte (except for indication specified in this policy);
- TruSkin;
- Unite Biomatrix;
- XCellerate;
- XWRAP/XWRAP ECM;
- Any other skin substitute not specified in this policy as medically necessary (according to criteria section) are considered experimental and investigational and unproven.

SUMMARY OF MEDICAL EVIDENCE [14-48]

The evidence suggests that skin substitutes appear to heal more chronic foot ulcers than standard wound care alone and may prevent amputation in patients with diabetes. Using skin substitutes may result in a lower incidence of wound infection and does not appear to present unique or serious safety concerns. Evidence suggests that more patients with chronic venous leg ulcers that do not heal with standard care alone experience complete healing when a bilayer human skin equivalent or allograft is used in addition to standard care. The evidence suggests that bioengineered skin substitutes for deep dermal burns appears to improve the long-term functional and cosmetic outcomes and increase quality of life. Benefits for other conditions using skin substitutes for wound healing have not been clearly demonstrated in robust clinical studies published in the peer reviewed medical literature. Evidence directly comparing different skin substitute products or types is extremely limited and insufficient to inform whether any one product or product type is superior to other products. Safety data were generally very limited but do not suggest skin substitutes are associated with serious harms or greater safety risks than standard care alone.

Burns

Burns can be full or partial thickness, and may cause significant disability depending on the depth and body surface area (BSA) affected. Autografts remain the best treatment for burns; however, skin substitutes are used as an adjunct or temporary replacement to autologous grafting on partial or full thickness freshly excised burns. Evidence for the use of skin substitutes for treating burns is limited; small study size, the fragility of burn victims, and the inability to control confounding factors contribute to the difficulty in study design and execution. In practice, some FDA-approved skin substitutes are in use based on anecdotal evidence only. Although there was poor reporting of methodology, evidence from the small trials evaluated in one systematic review suggested that skin substitutes (e.g., Biobrane, TransCyte, Dermagraft, allogenic cultured skin) were as safe and at least as efficacious as topical agents, dressings, or allografts for treating partial thickness burns (Pham et al., Burns 2007). [35] Less pain, shorter wound healing time, and shorter hospital stays were observed with skin substitutes when compared to silver sulphadiazine dressings in another review of lower quality studies. (Wasiak et al., Cochrane Database Syst Rev 2013). [45] FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated. FDA approved skin substitutes for the treatment of burns by the 501(k) process are based only on evidence consisting of small unblinded studies of poor quality. For full or partial thickness burns with greater than 30% BSA involvement, the FDA has set up a process to allow the use of skin substitutes for patients who have sustained extensive tissue loss which necessitates a life-saving intervention. This humanitarian device exemption allows a hospital-based internal review board to approve and oversee the treatment of patients who qualify under the exception. [52]

Diabetic Foot Ulcers

The International Consensus on the Diabetic Foot [13] defines a diabetic foot ulcer as a full thickness wound peripheral to the ankle that may include exposure of underlying structures and is a complication of diabetes. Diabetic foot ulcers are difficult to treat and have a high recurrence rate. Skin substitutes may be used as adjunctive treatment for full thickness, chronic diabetic foot ulcers which have failed to heal with conservative methods (e.g., dressings, off-loading, non-weight-bearing). Some skin substitutes may not be appropriate for wounds with exposed underlying structures, an active wound infection, or certain conditions (e.g., Charcot′s

arthropathy, allergy to xenograft source). In one multicenter, randomized trial, Dermagraft treatment for diabetic foot ulcers of greater than six weeks duration showed a 30% rate of healing in comparison to 18% healing when standard dressings were used (Marston et al., Diabetes Care). [32] In a meta-analysis reviewing the use of acellular regenerative tissue matrix treatment for diabetic foot ulcers, complete wound healing was seen in 43% of patients compared to 30% with continued conservative treatment. In the same study, Apligraft and Dermagraft showed a significant change in the wound; Hyalograft-3D will need more studies to prove efficacy (Teng et al., Diabetes Obes Metab 2010).[42] FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated (Felder et al., Plast Reconstr Surg 2012). [22]

Venous Leg Ulcers

Venous leg ulcers form secondary to venous obstruction or reflux and are generally located on the leg below the knee. The diagnosis is confirmed by imaging (e.g., duplex ultrasound, plethysmography, venography, venous pressure measurement) in addition to clinical presentation. Ankle brachial index (ABI) measurement is helpful to rule out arterial occlusive disease and can be indicative of sufficient oxygenated blood flow to the wound. Revascularization, if indicated, is performed prior to wound treatment (Gloviczki et al., Journal of Vascular Surgery 2011). [7] Skin substitutes are an adjunct to compression dressings to treat noninfected partial or full thickness skin ulcers due to venous insufficiency of greater than four weeks duration. Living cell-based skin substitute grafts have been shown to increase the success of complete wound healing when applied to venous ulcers (Felder et al., Plast Reconstr Surg 2012). [22] Bilayer tissue-engineered skin substitute grafts showed complete wound healing after six months in 63% of the venous leg ulcers treated compared to 49% healing using simple compression dressings in one large study (Jones et al., Cochrane Database Syst Rev 2013). [28] FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated.

TECHNOLOGY ASSESSMENT [4]

The Agency for Healthcare Research and Quality (AHRQ) Technology Assessment (2019-2020)[4]*:* This document describes skin substitute products commercially available in the United States used to treat chronic wounds, examine systems used to classify skin substitutes, identify and assess randomized controlled trials (RCTs), and suggest best practices for future studies. The report states: "74 commercially available skin substitutes were identified and categorized based on the Davison-Kolter classification system. Sixty-eight (92%) were categorized as acellular dermal substitutes, mostly replacements from human amniotic membranes and animal tissue sources. Three systematic reviews and 17 RCTs examined use of 13 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers and venous leg ulcers. Twenty-seven experimental ongoing clinical trials examined an additional 12 skin substitutes with similar classifications. Studies rarely reported clinical outcomes such as amputation, wound recurrence at least 2 weeks after treatment ended, and patient-related outcomes such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field is this Technical Brief's clearest implication."

Key findings in the 2019 document outlined include:

- 74 commercially available skin substitutes were identified to treat chronic wounds. The majority of these do not contain cells and are derived from human amniotic membrane (the inner layer of the placenta), animal tissue, or human cadaver skin.
- 17 randomized controlled trials and 3 systematic reviews were included and experimental ongoing clinical trials will have examined only 25 (34%) of these skin substitutes by early 2019.
- Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
- Future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow-up.

Key Findings for the 2020 update include:

The updated report states: "76 commercially available skin substitutes and categorized them based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and reported studies providing more clinically relevant data in this field are this Technical Brief's clearest implications."

- 76 commercially available skin substitutes to treat chronic wounds. The majority of these do not contain cells and are derived from human placental membrane (the placenta's inner layer), animal tissue, or donated human dermis.
- 22 RCTs and 3 systematic reviews were included and ongoing clinical trials found during examine approximately 25 (33%) of these skin substitutes.
- Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
- Future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow-up.

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL 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. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15272	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)
15273	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
15274	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)
15275	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; first 25 sq cm or less wound surface area
15276	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)
15277	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
15278	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)

HCPCS	**Description:**
	Codes for the skin substitute products: Medically Necessary:
C9250	Human plasma fibrin sealant, vapor-heated, solvent-detergent (Artiss), 2ml
Q4100	Skin substitute, not otherwise specified [Use for Biobrane, Epicel, OrCel, Suprathel]
Q4101	Apligraf per square centimeter
Q4102	Oasis wound matrix, per sq cm
Q4103	Oasis burn matrix, per sq cm
Q4104	Integra bilayer matrix wound dressing (BMWD), per sq cm
Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106	Dermagraft per square centimeter
Q4107	GraftJacket Regenerative Tissue Matrix
Q4108	Integra matrix per square centimeter
Q4121	TheraSkin, per sq cm
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cmr
Q4124	Oasis Ultra Tri-Layer per square centimeter
Q4131	EpiFix or epicord per square centimeter
Q4132	Grafix core and grafixpl core, per square centimeter

Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4151	AmnioBand or Guardian, per sq cm
Q4168	AmnioBand, 1 mg
Q4182	Transcyte per square centimeter
Q4186	Epifix, per square centimeter
	Codes for skin substitute products: Experimental, Investigational and Unproven. Please note new codes are may be added more frequently or at different intervals than policy updates therefore this list may not be all inclusive:
Q4100	Skin substitute, nos [Use for others not specified]
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per sq cm
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket xpress, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per sq cm
Q4116	Alloderm, per square centimeter
Q4117	Hyalomatrix, per sq cm
Q4118	Matristem micromatrix, 1mg
Q4123	AlloSkin RT, per sq cm
Q4125	Arthroflex, per square centimeter
Q4126	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm
Q4127	Talymed, per sq cm
Q4128	Flexhd, allopatch hd, or matrix hd per square centimeter
Q4130	Strattice tm, per square centimeter
Q4134	Hmatrix, per sq cm
Q4135	Mediskin, per sq cm
Q4136	E-Z Derm, per sq cm
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
Q4138	Biodfense dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	BioDFence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per square centimeter
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap DS or dry, per square centimeter

Q4152	DermaPure, per sq cm
Q4153	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per sq cm
Q4158	Kerecis Omega3, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, per square centimeter
Q4161	bio-ConneKt wound matrix, per sq cm
Q4162	Woundex flow, bioskin flow, 0.5cc
Q4163	Woundex, bioskin, per sq cm
Q4164	Helicoll, per square cm
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4169	Artacent wound, per sq cm
Q4170	Cygnus, per sq cm
Q4171	Interfyl, 1 mg
Q4173	Palingen or Palingen Xplus, per sq cm
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4175	Miroderm, per sq cm
Q4176	Neopatch or Therion, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter
Q4183	Surgigraft, 1 sq cm
Q4184	Cellesta or Cellesta Duo, per sq cm
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4187	Epicord, per square centimeter
Q4188	AmnioArmor, per sq cm
Q4189	Artacent ac, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4194	Novachor, per square centimeter
Q4195	PuraPly, per square cm
Q4196	PuraPly AM , per square cm

Q4197	Puraply XT, per square cm
Q4198	Genesis amniotic membrane, per square centimeter
Q4200	Skin te, per square centimeter
Q4201	Matrion, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-Gide, per sq cm
Q4204	Xwrap, per square centimeter
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid gf, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGraft, per sq cm
Q4210	Axolotl Graft or Axolotl DualGraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT-DUAL, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amniowrap2, per square centimeter
Q4222	ProgenaMatrix, per sq cm
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227	AmnioCoreTM, per sq cm
Q4228	BioNextPATCH, per sq cm
Q4229	Cogenex Amniotic Membrane, per sq cm
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per sq cm
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per sq cm
Q4235	AMNIOREPAIR or AltiPly, per sq cm
Q4236	carePATCH, per sq cm
Q4237	Cryo-Cord, per sq cm
Q4238	Derm-Maxx, per sq cm
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240	CoreCyte, for topical use only, per 0.5 cc

Q4241	PolyCyte, for topical use only, per 0.5 cc
Q4242	AmnioCyte Plus, per 0.5 cc
Q4244	Procenta, per 200 mg
Q4245	AmnioText, per cc
Q4246	CoreText or ProText, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm
Q4250	AmnioAmp-MP, per sq cm
Q4254	Novafix DL, per sq cm
Q4255	REGUaRD, for topical use only, per sq cm

ICD-10	Description: [For dates of service on or after 10/01/2015]
	Any/All

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Other Resources

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REVISION/REVIEW HISTORY:

4/23/20: New Policy
2/8/2021: Policy reviewed and clinical criteria was completely updated with additional and comprehensive wound specific recommendations for burns, diabetic foot ulcers and venous leg ulcers. Coding tables updated with all products available at time of this review. Contraindications and limitations sections updated. Guidelines and references sections revised, condensed and updated.