Tissue-Engineered Skin Substitutes

Policy Number: MM.06.018
Original Effective Date: 06/01/2012
Line(s) of Business: HMO; PPO
Current Effective Date: 06/01/2012
Section: Surgery
Place(s) of Service: Outpatient/Office

I. Description

Background

Tissue-engineered skin substitutes, also referred to as artificial skin, are bioengineered skin products that may be derived from human tissue (autologous or allogeneic), non-human tissue (xenographic), synthetic materials, or a composite of these materials.

Tissue-engineered skin substitutes may be either acellular or cellular. Acellular products (i.e., cadaveric human dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin products. One large category is non-healing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, non-healing lower extremity wounds represent an ongoing risk for infection, sepsis, limb amputation and death. Skin substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which tissue-engineered skin products might substitute for living skin grafts include certain post-surgical states such as breast reconstruction, in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts.
Regulatory Status

There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy. This list demonstrates the wide range of types of products available:

AlloDerm is an acellular dermal matrix (allograft) derived from donated human skin tissue supplied by U.S. compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration's (FDA) guidelines. Acellular tissue matrix is a tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. The processing removes the cellular components that can lead to rejection and infection. Since AlloDerm is regarded as minimally processed and not significantly changed in structure from the natural material, the FDA has classified it as banked human tissue.

AlloMax Surgical Graft is an acellular non-cross-linked human dermis allograft. It is classified as banked human tissue and does not require FDA approval.

Apligraf is a bilayered cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. It was FDA approved in 1998 for use in conjunction with compression therapy for the treatment of non-infected, partial and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy.

Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen applied to a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers and for use in the treatment of wounds related to dystrophic epidermolysis bullosa.

Graftjacket Regenerative Tissue Matrix is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is processed minimally to remove the epidermal and dermal cells while preserving dermal structure. It is regulated by the FDA as human tissue for transplantation.

Oasis Wound Matrix is a xenographic collagen scaffold derived from porcine small intestinal mucosa. It was cleared by the FDA's 510(k) process in 2000 for the management of partial and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

OrCel is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA pre-market approval for healing donor site wounds in burn victims and under a humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

This policy does not address products used in the treatment of burns, tendon/ligament repair or products supplied in an inpatient setting.
II. Criteria/Guidelines

A. AlloDerm is covered (subject to Limitations/Exclusions and Administrative Guidelines) in breast reconstructive surgery when one of the following criteria are met:
   1. There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required.
   2. There are viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis.
   3. The infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

B. Apligraf or Dermagraft is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers when all of the following criteria are met:
   1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
   2. The patient is on a diabetic management program and has adequate control of his/her diabetes with a hemoglobin A1c of less than eight or documented self-management of blood glucose with twice daily preprandial glucose levels less than 150; and
   3. Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities.

C. Apligraf or Oasis Wound Matrix is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency when all of the following criteria are met:
   1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
   2. Compression bandages and/or graduated compression garments have been consistently applied; and
   3. Leg elevation and exercise have been encouraged.

D. Dermagraft or OrCel is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of dystrophic epidermolysis bullosa.

* Standard wound therapy includes:
   - Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional.
   - Application of moist topical dressings
   - Debridement of necrotic tissue, if present
   - Treatment of infection, if present
   - Evaluation and provision of adequate nutrition
   - Management of diabetes mellitus, if applicable
   - Evaluation and management of peripheral artery disease, if applicable

III. Limitations/Exclusions

A. All other uses of allogeneic skin substitutes not listed under Criteria/Guidelines are not covered as their use has not been shown to improve health outcomes.
B. All other skin substitutes not listed under Criteria/Guidelines are not covered as their use is not known to improve health outcomes. This includes, but is not limited to:

- Allomax
- Allopatch HD
- Alloskin RT
- Arthroflex
- Cymetra
- E-Z Derm
- Flex HD
- Gammagraft
- Graftjacket Express injectable (not applicable when used in tendon repair)
- Graftjacket Regenerative Tissue Matrix (not applicable when used in tendon repair)
- Hyalomatrix
- MatriStem Micromatrix
- MatriStem Wound Matrix
- Memoderm
- Primatrix
- Strattice TM
- SurgiMend
- Talymed
- TissuMend
- Unite Biomatrix

IV. Administrative Guidelines

A. Precertification is required for the application of Apligraf, Dermagraft, OrCel and Oasis. Complete HMSA’s Precertification request and mail or fax the form as indicated. Include the following information:

1. Clinical notes documenting patient’s compliance with a diabetic management program.
2. The exact location of the ulcer and initial ulcer size.
3. Duration and description of the standard treatments that were tried and failed.
4. Documentation of the presence of dystrophic epidermolysis bullosa if this is the indication.

B. Alloderm does not require precertification. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.

C. Applicable codes:

<table>
<thead>
<tr>
<th>HCPSC Codes</th>
<th>Description</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4101</td>
<td>Apligraf, per sq. cm.</td>
</tr>
<tr>
<td>Q4102</td>
<td>Oasis wound matrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4106</td>
<td>Dermagraft, per sq. cm.</td>
</tr>
<tr>
<td>Q4116</td>
<td>AlloDerm</td>
</tr>
<tr>
<td>Q4124</td>
<td>Oasis Ultra tri-layer wound matrix, per sq. cm.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15271</td>
<td>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</td>
</tr>
<tr>
<td>15272</td>
<td>each additional 25 sq cm wound surface area, or part thereof</td>
</tr>
<tr>
<td>15273</td>
<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>
</tr>
<tr>
<td>15274</td>
<td>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</td>
</tr>
<tr>
<td>15275</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; first 25 sq cm or less wound surface area</td>
</tr>
<tr>
<td>15276</td>
<td>each additional 25 sq cm wound surface area, or part thereof</td>
</tr>
<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 infants and children</td>
</tr>
<tr>
<td>15278</td>
<td>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</td>
</tr>
</tbody>
</table>

D. HCPCS codes that do not meet payment determination criteria:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4107</td>
<td>Graftjacket, per sq. cm.</td>
</tr>
<tr>
<td>Q4110</td>
<td>PriMatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per sq. cm.</td>
</tr>
<tr>
<td>Q4112</td>
<td>Cymetra, injectable</td>
</tr>
<tr>
<td>Q4113</td>
<td>Graftjacket Express, injectable, 1cc</td>
</tr>
<tr>
<td>Q4115</td>
<td>Alloskin</td>
</tr>
</tbody>
</table>
V. Rationale:

This policy was developed based on a literature search using Medline and various other peer reviewed articles. Key literature, focusing on controlled trials, is described below.

Breast Reconstruction

AlloDerm

Controlled Studies: Preminger and colleagues evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study. (1) Forty-five patients had reconstruction with AlloDerm and 45 had standard reconstruction. Subjects were matched for expander size (+/-100 mL), history of irradiation, and indication for mastectomy. There were no significant differences in initial filling volume, mean number of postoperative expansions, mean rate of postoperative tissue expansion, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed.

In 2008 Colwell and Breuing reported on 10 patients who had mastopexy with dermal slings, 5 patients were given cadaveric (AlloDerm) and 5 were given autologous tissue. (2) Patients have maintained projection and breast base width after 6 months to 3 years. Thus, a number of case series have demonstrated that this approach can provide tissue coverage of implants and tissue expanders.

Uncontrolled Studies: Salzberg reported results on use of AlloDerm for reconstructive surgery on 76 breasts in 49 patients who underwent immediate reconstructive surgery after mastectomy in 2006. (3) Patients were considered good candidates if they had skin-sparing mastectomies or had adequate soft tissue coverage. The mean follow-up was 18 months (range, 3–52 months). The authors reported that patients had “decreased” post-surgical pain, and that, subjectively, physicians and patients were satisfied with the breast projection and desired symmetry. No serious postoperative complications were reported. Based on biopsies obtained at 2 and 6 months in 2 patients, fibroblast ingrowth and full vascularity were noted.
Breuning reported on use of the AlloDerm hammock in 43 patients and 67 breasts in 2007. (4) Indications for reconstructive surgery and use of the allograft were immediate expander-implant reconstruction (N=10), immediate silicone implant reconstruction (N=30), delayed expander-implant reconstruction (N=4), and revisional implant reconstruction for capsular contracture following capsulectomy (N=23). The article indicates that patients were included if AlloDerm was used in association with an implant or expander to reconstruct their breast. The authors reported that the AlloDerm hammock allowed complete coverage of the implant and symmetric positioning of the infra-mammary fold. In delayed reconstructions with existing skin redundancy at the mastectomy site, inferior epigastric tissue was recruited, and tissue expanders filled over 75% of the desired volume, thus decreasing the need for subsequent filling. One patient had implant extrusion and 2 had infections. No capsular contracture, hematoma, or seroma was observed at mean follow-up of approximately 1.5 years (range, 6 months to 3 years). The authors concluded that implant reconstruction with an inferolateral AlloDerm hammock facilitates positioning of the implant in immediate or revisional breast reconstruction and simplifies expander-implant reconstruction.

AlloDerm has also been reported in nipple reconstructive surgery. (5) This report involves a case series on 30 nipple reconstructive procedures performed at one institution. The authors conclude that use of an AlloDerm graft core is a safe technique for “improving the long-term maintenance of nipple projection.”

Bindingnavele et al. reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates. (6) Rates for wound infection, expander removal, hematoma, and seroma were 3.1%, 1.5%, 1.5%, and 4.6%, respectively. The authors concluded that based on low rates of complications and good cosmetic outcomes, the technology should be in the repertoire of plastic surgeons, and that follow-up is required to evaluate long-term outcomes.

**Surgical Repair of Hernias**

**AlloDerm**

Gupta et al. compared the efficacy and complications associated with the use of AlloDerm and Sugisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. (7) The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine sub-mucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7-10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

In 2007, Espinosa-de-los-Monteros and colleagues retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. (8) They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when
adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

The limited evidence available at this time does not support the use of AlloDerm in hernia repair.

**Diabetic Lower Extremity Ulcers**

**Apligraf**

In 2001, Veves and colleagues reported on a randomized prospective study on the effectiveness of Graftskin (Apligraf), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. (9) The study involved 24 centers in the US, 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot-offloading, was provided in both groups. Graftskin was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Graftskin group. The authors concluded that application of Graftskin for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management. (10)

In 2010, Steinberg and colleagues reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. (11) The design and patient population of this study were similar to the 208-subject United States study (described above) which led to FDA approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least two weeks were enrolled in these prospective, multicenter, randomized, controlled, open-label studies that compared Apligraf use in conjunction with standard therapy (sharp debridement, standard wound care, and off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the two studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration that was significantly longer in the European study (21 months, compared to 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the two studies. Efficacy measures demonstrated superiority of Apligraf treatment over control treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared to 34.3% (46/134) of control subjects (p=0.0005), and Apligraf subjects had a significantly shorter time to complete wound closure (p=0.0004). The authors concluded that both the EU and US studies exhibited superior efficacy and
comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating DFU.

In 2010, Kirsner and colleagues reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. (12) The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy i.e., Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001), and 40.0% more likely to heal than those first treated with platelet releasate (p=0.01). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

**Dermagraft**

A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. Over the course of the 12-week study patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared to 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%).

**GraftJacket Regenerative Tissue Matrix**

Brigido et al. reported a small (n=40) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. (13) Control patients received conventional therapy with debridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary 1 month results showed that after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%) and depth (89% vs. 25%). All of the grafts incorporated into the host tissue.

In 2009, Reyzelman et al. reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care in 86 patients with diabetic foot ulcers. (14) Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm2 in the GraftJacket group and 5.1 cm2 in the control group. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in non-healing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7
weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for GraftJacket (range, 1 – 12) and 7.0 weeks for control (range 2 – 12). Kaplan-Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if GraftJacket Regenerative Tissue Matrix improves health outcomes in this population.

Oasis Wound Matrix

Niezgoda and colleagues compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel. (15) This was an industry-sponsored randomized controlled multicenter trial conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the non-inferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These post-hoc findings are considered hypothesis generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current standard of care.

Lower Extremity Ulcers due to Venous Insufficiency

Apligraf

Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. (16) A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean 3.3) times per patient during the initial 3 weeks. The primary endpoints were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6 months’ follow-up, the percentage of patients healed was increased with Apligraf (63% vs. 49%) and the median time to complete wound closure was reduced (61 vs. 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1000 mm2) and deeper ulcers and ulcers of more than 6 months’ duration. There were no symptoms or signs of rejection and the occurrence of adverse events were similar in both groups. This study was reviewed in a 2001 TEC
Assessment, which concluded that Apligraf (graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management. (10)

**Oasis Wound Matrix**

In 2005, Mostow et al. reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus standard of care in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. (17) Healing was assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to achieve healing than those in the standard care group. Patients in the standard care group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix and seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described two comparative studies of the Oasis matrix for mixed arterial venous and venous ulcers. In a 2007 quasi-randomized study, Romanelli et al. compared the efficacy of two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). (18) A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week and the dressings were changed more than once a week only if necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean of 6.4 vs. 2.4 days), reduced pain on a 10 point scale (3.7 vs. 6.2) and improved patient comfort (2.5 vs. 6.7).

In a 2010 trial, Romanelli et al. compared Oasis with a moist wound dressing in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. (19) The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks compared to 65% of the standard of care group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard of care group. Treatment with Oasis also increased the time to dressing change (5.2 vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

**Dystrophic Epidermolysis Bullosa**

Dermagraft is FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa.

OrCel is approved by a HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

As this is a rare disorder, it is unlikely that there will be randomized controlled trials to evaluate whether Dermagraft or OrCel improve health outcomes for this condition.
Summary

Overall, the number of tissue-engineered skin substitutes is large but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. A few comparative trials have been identified for use in lower extremity ulcers (diabetic or venous). In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by either clinical input or by an FDA HDE.

Breast Reconstruction

Given the extensive data from case series as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of AlloDerm may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis’ or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

Surgical Repair of Hernias

The limited evidence available does not support the efficacy of any tissue-engineered skin substitute for surgical repair of hernias. Therefore, this use is not covered.

Diabetic Lower Extremity Ulcers

Randomized controlled trials have demonstrated the efficacy of Apligraf and Dermagraft over the standard of care. Use of these products may be considered medically necessary for the treatment of diabetic lower extremity ulcers.

Lower Extremity Ulcers due to Venous Insufficiency

Randomized controlled trials have demonstrated the efficacy of Apligraf and Oasis Wound Matrix over the standard of care. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency.

Dystrophic Epidermolysis Bullosa

Dermagraft and OrCel have received approval via a Humanitarian Device Exemption (HDE). As this is a rare disorder and it is unlikely that there will be randomized controlled trials, these products are considered medically necessary.

All other uses of the tissue-engineered skin substitutes do not meet payment determination criteria.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is
intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References