Medical Policy
Bio-Engineered Skin and Soft Tissue Substitutes

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Policy Number: 663
BCBSA Reference Number: 7.01.113

Related Policies
- Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions, #186

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Breast reconstructive surgery using allogeneic acellular dermal matrix products* (ie, AlloDerm®, AlloMax™, DermaMatrix™, FlexHD®, GraftJacket®) may be MEDICALLY NECESSARY:
- 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
- The infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

Treatment of chronic, noninfected, full-thickness diabetic lower extremity ulcers using the following tissue-engineered skin substitutes may be MEDICALLY NECESSARY:
- Apligraf®**
- Dermagraft®**

Treatment of chronic, non-infected, partial- or full-thickness lower extremity skin ulcers due to venous insufficiency, which have not adequately responded following a one-month period of conventional ulcer therapy, using the following tissue-engineered skin substitutes may be MEDICALLY NECESSARY:
- Apligraf®**
- Oasis™ Wound Matrix***

Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be MEDICALLY NECESSARY:
• OrCel™ (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the FDA)****

Treatment of second- and third-degree burns using the following tissue-engineered skin substitutes may be MEDICALLY NECESSARY:
• Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA)****
• Integra Dermal Regeneration Template™**
• TransCyte™**

*Banked Human Tissue
** FDA PMA approved
*** FDA 510(k) cleared
**** FDA-approved under a humanitarian device exemption (HDE)

All other uses of the bio-engineered skin and soft tissue substitutes listed above are INVESTIGATIONAL.

All other skin and soft tissue substitutes not listed above are INVESTIGATIONAL, including, but not limited to:
• ACell® UBM Hydated Wound Dressing
• ACell® UBM Lyophilized Wound Dressing
• AlloPatch HD™
• AlloSkin™
• AlloSkin™ RT
• Amniofix®
• Aongen™ Collagen Matrix
• ArthroFlex™ (FlexGraft)
• Atlas Wound Matrix
• Avagen Wound Dressing
• Avaulta Plus™
• Biobrane®
• BioDfence/BioDfactor
• CellerateRX®
• Collagen Sponge (Innocoll)
• Collagen Wound Dressing (Oasis Research)
• Collaguard®
• CollaSorb™
• CollaWound™
• Collexa®
• Collieva®
• Conexa™
• Coreleader Colla-Pad
• CorMatrix®
• CRXa™
• Cymetra®
• Dermadapt™ Wound Dressing
• DressSkin
• Durepair Regeneration Matrix®
• Endoform Dermal Template™
• ENDURAgent™
• Epifix® Excellagen
• E-Z Derm™
- FortaDerm™ Wound Dressing
- GammaGraft
- Grafix® core
- Grafix® prime
- GraftJacket® Xpress, injectable
- HA Absorbent Wound Dressing
- Helicoll
- Hyalomatrix® (Laserskin®)
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix
- Integra™ Bilayer Wound Matrix
- JaloSkin®
- MatriDerm®
- MatriStem® Burn Matrix
- MatriStem® Micromatrix
- MatriStem® Wound Matrix
- Matrix Collagen Wound Dressing
- Matrix HD™
- MediHoney®
- Mediskin®
- MemoDerm™
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Matrix
- Permacol™
- PriMatrix
- Primatrix™ Dermal Repair Scaffold
- Puros® Dermis
- Repliform®
- Repriza™
- SIS Wound Dressing II
- SS Matrix™
- Stimulen™ Collagen
- StrataGraft
- Strattice™ (xenograft)
- Suprathe®
- SurgiMend®
- Talymed®
- TenoGlide™
- TheraForm™ Standard/Sheet
- TheraSkin® Unite™
- Unite® Biomatrix
- Veritas® Collagen Matrix

Medicare HMO Blue™ and Medicare PPO Blue™ Members

Local Coverage Determination (LCD): Biologic Products for Wound Treatment and Surgical Interventions (L30135)

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
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<tr>
<td>Medicare PPO Blue℠</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code 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>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>
</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>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>
</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>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>
</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 of infants and children</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>15777</td>
<td>Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>HCPCS Codes</td>
<td>Code Description</td>
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<tr>
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</tr>
<tr>
<td>C9354</td>
<td>Acellular pericardial tissue matrix of nonhuman origin (Veritas), per square centimeter</td>
</tr>
<tr>
<td>C9358</td>
<td>Dermal substitute, native, nondenatured collage, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
</tr>
<tr>
<td>C9360</td>
<td>Dermal substitute, native, nondenatured collage, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
</tr>
<tr>
<td>C9363</td>
<td>Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm</td>
</tr>
<tr>
<td>C9364</td>
<td>Porcine implant, Permacol, per square centimeter</td>
</tr>
<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>Q4103</td>
<td>Oasis burn matrix, per sq cm</td>
</tr>
<tr>
<td>Q4104</td>
<td>Integra dermal regeneration template (DRT), per sq cm</td>
</tr>
<tr>
<td>Q4105</td>
<td>Dermagraft, per sq cm</td>
</tr>
<tr>
<td>Q4106</td>
<td>GRAFTJACKET, per sq cm</td>
</tr>
<tr>
<td>Q4107</td>
<td>Integra bilayer matrix wound dressing (BMWD), per sq cm</td>
</tr>
<tr>
<td>Q4108</td>
<td>PriMatrix, per sq cm</td>
</tr>
<tr>
<td>Q4110</td>
<td>Integra matrix, per sq cm</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per sq cm</td>
</tr>
<tr>
<td>Q4112</td>
<td>Cyrograft, injectable, 1 cc</td>
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<tr>
<td>Q4113</td>
<td>GRAFTJACKET XPRESS, injectable, 1cc</td>
</tr>
<tr>
<td>Q4114</td>
<td>Integra flowable wound matrix, injectable, 1 cc</td>
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<tr>
<td>Q4115</td>
<td>AlloSkin, per sq cm</td>
</tr>
<tr>
<td>Q4116</td>
<td>AlloDerm, per sq cm</td>
</tr>
<tr>
<td>Q4117</td>
<td>HYALOMATRIX, per sq cm</td>
</tr>
<tr>
<td>Q4118</td>
<td>MatriStem micromatrix, 1 mg</td>
</tr>
<tr>
<td>Q4119</td>
<td>MatriStem Wound Matrix, PSMX, RS, or PSM, per sq cm</td>
</tr>
<tr>
<td>Q4120</td>
<td>MatriStem burn matrix, per sq cm</td>
</tr>
<tr>
<td>Q4122</td>
<td>DermACELL, per sq cm</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per sq cm</td>
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<tr>
<td>Q4124</td>
<td>OASIS ultra tri-layer wound matrix, per sq cm</td>
</tr>
<tr>
<td>Q4125</td>
<td>Arthroflex, per sq cm</td>
</tr>
<tr>
<td>Q4126</td>
<td>MemoDerm, per sq cm</td>
</tr>
<tr>
<td>Q4127</td>
<td>Talymed, per sq cm</td>
</tr>
<tr>
<td>Q4128</td>
<td>FlexHD or AllopatchHD, per sq cm</td>
</tr>
<tr>
<td>Q4129</td>
<td>Unite biomatrix, per sq cm</td>
</tr>
<tr>
<td>Q4130</td>
<td>Strattice TM, per sq cm</td>
</tr>
<tr>
<td>Q4131</td>
<td>Epifix, per square centimeter</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix core, per square centimeter</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix prime, per square centimeter</td>
</tr>
<tr>
<td>Q4134</td>
<td>Hmatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
</tr>
<tr>
<td>Q4136</td>
<td>Ez-derm, per square centimeter</td>
</tr>
<tr>
<td>Q4137</td>
<td>Amnioexcel or biodexcel, per square centimeter</td>
</tr>
<tr>
<td>Q4138</td>
<td>Biodfence dryflex, per square centimeter</td>
</tr>
<tr>
<td>Q4139</td>
<td>Amniomatrix or biodmatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>Biodfence, per square centimeter</td>
</tr>
<tr>
<td>Q4141</td>
<td>Alloskin ac, per square centimeter</td>
</tr>
<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
</tr>
<tr>
<td>Q4145</td>
<td>Epifix, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4146</td>
<td>Tensix, per square centimeter</td>
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</tbody>
</table>
Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and to aid healing of lower-extremity ulcers and severe burns. Acellular dermal matrix products are also being evaluated in the repair of a variety of soft tissues.

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (ie, 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 (eg, 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 and soft tissue products. One large category is nonhealing 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, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bio-engineered skin products might substitute for living skin grafts include certain postsurgical 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. Second- and third-degree burns are another situation in which artificial skin products may substitute for auto- or allografts. 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. Acellular dermal matrix (ADM) products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and a variety of other conditions.

Summary
Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions. Overall, the number of bio-engineered skin and soft-tissue 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) and for treatment of burns. 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 humanitarian device exemption (HDE).

Breast Reconstruction
Given the extensive data from controlled cohorts and case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of allogeneic acellular dermal matrix (ADM) products (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, GraftJacket) 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 postmastectomy skin flaps that are at risk of dehiscence or necrosis, or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

**Interpositional Graft after Parotidectomy**
Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional ADM graft. Neither study described the method of group assignment or blinding of patients and assessors. In addition, clinical input regarding the use of an interpositional spacer after parotidectomy was not uniform. Therefore, bio-engineered skin and soft tissue substitutes are considered investigational to fill in contour defects and prevent Frey syndrome after parotidectomy.

**Tendon Repair**
One small RCT was identified that found improved outcomes with GraftJacket acellular human dermal matrix for rotator cuff repair. Although these results are promising, additional study with a larger number of subjects is needed. Therefore, this use is considered investigational.

**Fistula Repair**
One RCT was identified that used an ADM product that has not been cleared for marketing in the U.S. Therefore, the use of this product for fistula repair is considered investigational.

**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 considered investigational.

**Oral Surgery**
Use of acellular human dermal matrix (AlloDerm) has been reported for root coverage therapy and oral cavity reconstruction following surgical removal of tumors. Although AlloDerm may possibly result in less scar contracture, results to date have not shown an improvement over the standard of care. Therefore, this use is considered investigational.

**Laryngoplasty**
The effect of micronized AlloDerm (Cymetra) in laryngoplasty has been reported in case series. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

**Tympanoplasty**
AlloDerm has been compared with native tissue grafts in a non-RCT. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

**Diabetic Lower-Extremity Ulcers**
RCTs 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. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Lower-Extremity Ulcers Due to Venous Insufficiency**
RCTs 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. In a large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population, and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Dystrophic Epidermolysis Bullosa
OrCel has received approval via an HDE. As this is a rare disorder and it is unlikely that there will be RCTs, OrCel is considered medically necessary for this indication.

Ocular Burns
Evidence is insufficient to evaluate the efficacy of human amniotic membrane for ocular burns. This is considered investigational.

Nonocular Burns
Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. This treatment may be considered medically necessary according to the HDE indications. Comparative studies have demonstrated improved outcomes for Integra Dermal Regeneration Template and TransCyte for the treatment of burns; therefore, these are considered medically necessary.

Traumatic Wounds
Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint, and/or tendon. Controlled trials are needed to evaluate this product/indication.

All other uses of the bio-engineered skin and soft-tissue substitutes are considered investigational.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2014</td>
<td>Updated to add new HCPCS codes Q4137-Q4149.</td>
</tr>
</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


