Important note
Even though this policy may indicate that a particular service or supply may be considered covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Senior Care members, this policy will apply unless Medicare policies extend coverage beyond this Medical Policy & Criteria Statement. Senior Care policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website.

SERVICE: Biologics for Wound Care and Procedures

PRIOR AUTHORIZATION: Required in some instances

POLICY: This policy outlines the coverage of a heterogeneous group of products/substances that have been used to treat conditions such as diabetic and venous wound ulcers, burns, arthritic conditions, and fractures. The policy finds a vast majority of these treatments investigational in nature.

Biologics used in procedures (not medication), e.g.
- Platelet Rich Plasma (PRP)
- Skin Substitutes/Dermal matrix (SS/DM)
- Mesenchymal stem cells (MSC)
- Recombinant human bone morphogenic protein (BMP)
- Amniotic membrane transplant (AMT) for ophthalmologic procedures

Materials for Wound Care and Burns:

Skin Substitutes/Dermal matrix may be considered medically necessary in the following situations:

1. Acellular dermal matrix is considered medically necessary for either of the following uses:
   a. Surgical repair of complex abdominal wall wounds (e.g., due to infection, fascial defect, etc.); OR
   b. Breast reconstruction surgery.
   **Note:** Prior authorization is not necessary when an unanticipated need for acellular dermal matrix arises during a surgical procedure. However, the use of acellular dermal matrix under those circumstances may be reviewed retrospectively for medical necessity.

2. Apligraf® (Q4101) is considered medically necessary for a total of five (5) applications for either of the following indications:
   a. Venous insufficiency skin ulcers with ALL the following characteristics:
      - Chronic, non-infected, partial or full thickness ulcers due to venous insufficiency; AND
      - Standard therapeutic compression also in use; AND
      - At least one month of conventional ulcer therapy (such as standard dressing changes, and standard therapeutic compression) has been ineffective; OR
   b. Diabetic foot ulcers with all the following characteristics:
      - Full-thickness neuropathic diabetic foot ulcers; AND
• Extends through the dermis but without tendon, muscle, joint capsule, or bone exposure; AND
• At least three weeks of conventional ulcer therapy (such as surgical debridement, complete off-loading and standard dressing changes) has been ineffective.

3. Dermagraft® (Q4106) is considered medically necessary when used for either of the following indications:
   a. The treatment of full-thickness diabetic foot ulcers of greater than six weeks duration that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure; OR
   b. When used on wounds with dystrophic epidermolysis bullosa.

4. Integra® Bilayer Matrix Wound Dressing (Q4104) is considered medically necessary in the post-excisional treatment of full-thickness or deep partial-thickness burns when autografting is not feasible due to the individual's weakened physiological condition or a lack of suitable healthy tissue.

5. OrCel™ (no specific code) is considered medically necessary in children with recessive dystrophic epidermolysis bullosa who are undergoing reconstructive hand surgery.

6. TransCyte™ (no specific code) is considered medically necessary as a temporary wound covering to treat second and third degree burns.

7. Oasis Wound Matrix (Q4102) may be considered medically necessary for treatment of difficult-to-heal chronic venous or diabetic partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of at least 6 weeks duration.

8. Arthroflex (FlexGraft) (Q4125) for wound care is considered experimental and investigational because there is inadequate evidence in the peer-reviewed medical literature to support its clinical effectiveness.

9. See list below for other coverage.

Materials for Orthopedic Conditions:

1. Platelet Rich Plasma (PRP): Autologous blood-derived growth factors (i.e. platelet rich plasma) are considered investigational.

2. Stem cells and Mesenchymal stem cells (MSC).
   • Mesenchymal stem cell therapy is considered investigational and NOT a covered benefit for treatment of orthopedic indications.
   • Brain tissue transplantation, or stem-cell neuro-transplantation for treatment of Parkinson’s Disease (embryonic or fetal allograft or auto-transplantation) is considered experimental and investigational and NOT a covered benefit.

3. Recombinant human Bone Morphogenic Protein (rhBMP-2 or rhBMP-7 only)
   Currently 2 rhBMPs have FDA approval for specific uses. They are:
• OP-1TM (Osteogenic Protein-1™ Implant,) consists of rhBMP-7 and bovine collagen which is reconstituted with saline to form a paste or putty (with carboxymethylcellulose added).
• The InFuse® system is rhBMP-2 (dibotermin alfa) on an absorbable collagen sponge carrier.

4. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) is considered medically necessary for:
   • anterior lumbar interbody fusion (ALIF) procedure, (Not PLIF or TLIF- see below); OR
   • posterolateral lumbar intertransverse fusion procedure; OR
   • open fracture of the tibial shaft, which has been stabilized with intramedullary nail fixation after appropriate wound management.

5. The use of recombinant human bone morphogenetic protein-7 (rhBMP-7) is considered medically necessary for:
   • Treatment of tibial fracture nonunions after 7.5 months of conservative therapy, including electrical bone growth stimulation, when autologous bone graft is not feasible; or
   • As an alternative to autograft in compromised individuals requiring revision of posterolateral lumbar intertransverse fusion, when autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

6. The use of recombinant human bone morphogenetic protein-2 or recombinant human bone protein-7 is considered experimental and investigational for conditions that do not meet the above criteria, including but not limited to:
   • cervical or thoracic spinal fusion procedures;
   • posterior lumbar interbody fusion (PLIF) or transforaminal lumbar interbody fusion (TLIF);
   • As management of early stages of osteonecrosis of the vascular head or femoral shaft;
   • As an adjunct to distraction osteogenesis (Ilizarov procedure);
   • Craniofacial applications including, but not limited to, periodontal defect regeneration, cleft palate repair, cranial defect repair, restoration and maintenance of the alveolar dental ridge.

7. Amniotic Membrane Transplantation may be considered MEDICALLY necessary for the following ophthalmologic conditions after failure of conservative treatment:
   • Chemical and thermal injuries
   • Conjunctivochalasis
   • Conjunctival surface reconstruction
   • Corneal ulceration
   • Herpes zoster ophthalmicus
   • Limbal stem cell deficiency (partial or total): combined with stem cell graft
   • Persistent epithelial defects
   • Pterygium surgery
• Stevens-Johnson Syndrome
• Symblepharon lysis
• Symptomatic bullous keratopathy
• Trabeculectomy: bleb leakage or revision
  EpiFix (amniotic membrane) (Q4145)

8. **Artiss** (C9250) Human Fibrin Sealant may be considered medically necessary for the treatment of individuals with severe burns.

Artiss fibrin sealant is considered experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

**All other products and indications, including orthopedic, are considered experimental and investigational** because there is inadequate evidence in the peer-reviewed medical literature to support their clinical effectiveness.

**Coverage Summary:**

<table>
<thead>
<tr>
<th>Wound Care/Burn</th>
<th>Code</th>
<th>Orthopedic/Other Conditions</th>
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<tr>
<td>Acellular dermal matrix</td>
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<td>rhBMP-2 or rhBMP-7 only</td>
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<td>Skin substitute, NOS (OrCel, TransCyte)</td>
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<td>Integra® Bilayer Matrix Wound Dressing</td>
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<tr>
<td>Amniotic Membrane Transplantation</td>
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<td></td>
<td>For ophthalmologic conditions – see indications above</td>
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<td>EpiFix</td>
<td>Q4145</td>
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**MEDICAL COVERAGE POLICY**

**SERVICE:** Biologicals for Wound Care and Procedures

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<td>04/18/2018</td>
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Materials considered experimental and investigational because there is inadequate evidence in the peer-reviewed medical literature to support their clinical effectiveness:

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<thead>
<tr>
<th>Code</th>
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<tr>
<td>C9358</td>
<td>Dermal substitute, native, non-denatured collagen (SurgiMend Collagen Matrix)</td>
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<tr>
<td>C9360</td>
<td>Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix)</td>
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<td>C9364</td>
<td>Porcine implant, Permacol</td>
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<td>Oasis Burn Matrix</td>
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<tr>
<td>Q4108</td>
<td>Integra Matrix</td>
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<td>PriMatrix,</td>
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<td>Q4111</td>
<td>GammaGraft</td>
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<td>Cymetra, injectable</td>
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<td>Q4113</td>
<td>GRAFTJACKET XPRESS</td>
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<td>Integra Flowable Wound Matrix</td>
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<td>HYALOMATRIX</td>
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<td>Arthroflex</td>
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<td>Talymed</td>
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<td>Q4129</td>
<td>Unite biomatrix</td>
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<td>E-Z Derm</td>
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<td>Q4137</td>
<td>Amnioexcel or biodexcel</td>
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<tr>
<td>Q4138</td>
<td>Biodfence dryflex</td>
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<tr>
<td>Q4139</td>
<td>Amniomatrix or biodmatrix, injectable</td>
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<tr>
<td>Q4140</td>
<td>Biodfence</td>
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<td>AlloSkin AC</td>
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<td>Repriza</td>
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<td>Q4147</td>
<td>Architect, architect PX, or architect FX, extracellular matrix</td>
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<td>Q4149</td>
<td>Excellagen</td>
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OVERVIEW:

1. Platelet-rich plasma:

   PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. In addition, platelet-rich plasma has also been proposed as a primary treatment of miscellaneous conditions such as epicondylitis, plantar fasciitis and Dupuytren’s contracture.

   Typically the platelet-rich material is injected into joint area with the goal of accelerating the healing process. A meta-analysis of 10 trials assessing the effect of PRP injections in patients with knee OA found a significant difference in pain scores in the PRP-treated groups(8). However, the majority of the trials revealed a high likelihood of biases, and only one of the trials compared PRP injections with placebo. No trials have examined the structural effects of PRP in OA joints. There is a lack of standardization of the preparations of PRP amongst the trials, with varying concentration of platelet, frozen versus fresh preparations, and the filtration of white cells. The clinical trials have yet to conclusively demonstrate efficacy of the treatment. The available controlled studies do not provide consistent evidence that PRP improves outcomes in patients with ACL injury. Three RCTs found that PRP did not provide any significant benefits as a treatment for rotator cuff injuries, Achilles tendinopathy, or Achilles tendon rupture.
2. Skin substitutes/Dermal matrix:

Skin substitutes can be biological or synthetic substitutes. These products may be derived from allogeneic, xenographic, synthetic, or any combination of these. The biological skin substitutes have a more intact extracellular matrix structure, while the synthetic skin substitutes can be synthesized on demand. Both have advantages and disadvantages. The biological skin substitutes form a more natural new dermis and allow epithelialization because of the presence of a basement membrane.

Wound: The published evidence regarding the safety and efficacy of biological tissue-engineered skin substitutes is limited, and does not clearly demonstrate a benefit versus optimal standard wound care. No studies provided an adequate direct comparison of the different skin substitute products. More research is needed to compare different skin substitutes and to determine appropriate patient selection criteria.

Breast: Dermal matrices are considered a standard-of-care with breast reconstruction, with fewer complications and better results. Early literature focused on AlloDerm brand of acellular dermal matrix, as the initial product. Recent literature comparing acellular dermal matrix products conclude there is no significant difference among products (see, e.g., Ibrahim, et al., 2013; Cheng, et al., 2012).

3. Mesenchymal skin cells:

The American Academy of Orthopedic Surgeons (2007) provides information on stem cells:

Bone marrow stromal cells are mesenchymal stem cells that, in the proper environment, can differentiate into cells that are part of the musculoskeletal system. They can help to form trabecular bone, tendon, articular cartilage, ligaments and part of the bone marrow.

At this point, stem cell procedures in orthopedics are still at an experimental stage. Most procedures are performed at research centers as part of controlled clinical trials.

4. Recombinant human Bone Morphogenic Protein rhBMPs:

Osteogenic proteins or bone morphogenetic proteins (BMPs) are bone-matrix polypeptides that induce a sequence of cellular events leading to the formation of new bone. Some of the potential clinical applications of BMPs are: (i) as a bone graft substitute to promote spinal fusion and to aid in the incorporation of metal implants, (ii) to improve the performance of autograft and allograft bone, and (iii) as an agent for osteochondral defects.

Recombinantly produced human osteogenic protein-1 (OP-1), also known as BMP-7, was developed by Stryker and approved by the Food and Drug Administration (FDA) as a Humanitarian Use Device (HUD).

The INFUSE Bone Device (Medtronic Sofamor Danek) includes rhBMP-2 in a collagen absorbable sponge and a titanium spinal cage, and has been approved for spinal fusion in persons with single-level degenerative disc disease from L4 to S1, anterior approach only, after failure of 6 months of conservative treatment. Studies showed clinically equivalent fusion rates between the groups using INFUSE and autologous bone, with similar outcomes in terms of back pain, leg pain, disability and neurological status.

5. Amniotic Membrane transplant:
Ocular injuries due to trauma or disease that do not respond to conservative treatment may benefit from the use of AMT. The amniotic membrane has properties that are helpful in wound healing, particularly in ocular injuries. The amniotic membrane is the inner layer of the fetal sac, a stromal matrix, with a thick collagen layer and a single layer of epithelium. It suppresses growth factor to minimize scar formation and promotes cellular migration for improved healing.

MANDATES: None

SUPPORTING DATA:

CODES:

Important note: CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

| CPT Codes: | Application of skin substitute |
| CPT Not Covered: |
| HCPCS Codes | C9250 – Artiss human fibrin sealant  
Q4100 – Skin substitute, not otherwise classified  
Q4101 – Apligraf  
Q4102 – Oasis Wound Matrix  
Q4104 – Integra Bilayer Matrix Wound Dressing  
Q4106 – Dermagraft  
Q4116 – AlloDerm (acellular dermal matrix)  
Q4145 – Epifix (CORNEA ONLY) |
| HCPCS Codes Not covered | C9358, C9360, C9364, Q4103, Q4108, Q4110, Q4111, Q4112, Q4113, Q4114, Q4115, Q4117, Q4119, Q4121, Q4122, Q4123, Q4124, Q4125, Q4126, Q4127, Q4129, Q4130, Q4134, Q4135, Q4136, Q4137, Q4138, Q4139, Q4140, Q4141, Q4142, Q4143, Q4145, Q4147, Q4149, Q4150, Q4151, Q4152, Q4153, Q4154, Q4155, Q4156, Q4157, Q4158, Q4159, Q4160, Q4166, Q4167, Q4168, Q4169, Q4170, Q4171, Q4172, Q4173, Q4174, Q4175 |
| ICD10 codes | Platelet Rich Plasma  
M72.2 - Plantar fascial fibromatosis  
M76.5 - Patellar tendinitis  
M76.6 - Achilles tendinitis  
M77.1 - Lateral epicondylitis  
S46.0 - Injury of tendon of the rotator cuff of shoulder  
S76.1 - Injury of quadriceps tendon and muscle  
S83.4 - Sprain and strain involving fibular collateral ligament of knee  
S83.5 - Sprain and strain involving anterior cruciate ligament of knee  
S86.0 - Injury of Achilles tendon  
Bone morphogenetic protein  
M45.x* - Ankylosing spondylitis  
M47.x* - Spondylosis  
M50.x* - Cervical disc disorders  
M51.x* - Other intervertebral disc disorders  
S82.x* - Fracture of tibia |
CMS:
Platelet Rich Plasma: No NCD or LCD found

CMS issued its third non-coverage determination 8/2/2012, stating: “In summary, we conclude that PRP for Medicare beneficiaries with chronic non-diabetic, pressure, and/or venous wounds is not reasonable and necessary under §1862(a)(1)(A).”

However, proposed CMS coverage: “an autologous blood-derived product, will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when” the patient is enrolled in a randomized clinical trial that is CMS approved via CED (Coverage with Evidence Development.)

Skin Substitutes/Dermal matrix:
- LCD L35041; LCD Title: Application of BIOENGINEERED Skin Substitutes to Lower Extremity Chronic Non-Healing Wounds
- LCD L35125; LCD Title: Wound Care

Bone morphogenetic protein: No NCD or LCD found

In 2010, CMS published a technology assessment of the on-label and off-label use of rhBMP, which came to the following conclusions (Ratko et al., 2010):

- Strength of the body of evidence supporting improved outcomes with on-label use of rhBMP-2 (Infuse) was graded as moderate.
- Strength of the body of evidence supporting improved radiographic fusion success with off-label use of rhBMP-2 in fusion of the lumbar sacral spine was graded as moderate; the strength of other outcomes was graded as low.
- There was insufficient evidence to reach conclusions concerning radiographic fusion or associated changes in neck disability scores with the off-label use of rhBMP-2 in anterior cervical spinal fusion.
- There was insufficient evidence to reach conclusions concerning outcomes with on-label use of rhBMP-7 (OP-1) or with off-label use of rhBMP-7 in fusion of the lumbar sacral spine.
- Evidence on BMP-specific adverse events is insufficient to draw conclusions of safety in most settings; however, there is moderate evidence that off-label use of rhBMP-2 in anterior cervical spinal fusion increases cervical swelling and related complications.
- Quality of reporting in the studies reviewed was variable and inconsistent, in particular with respect to attribution of adverse events to BMP use and the use of standardized or validated instruments to collect adverse events.

Amniotic membrane transplant: No NCD or LCD found

POLICY HISTORY:

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REFERENCES:
The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the
Reference for Platelet Rich Plasma


Reference for skin/dermal substitutes


Reference for mesenchymal stem cells

### MEDICAL COVERAGE POLICY

**SERVICE:** Biologicals for Wound Care and Procedures

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#### Reference for recombinant human bone morphogenetic protein


#### Reference for amniotic membrane transplant for ophthalmologic procedures