Amniotic Membrane and Amniotic Fluid

Policy #  00458  
Original Effective Date:  08/19/2015  
Current Effective Date:  04/24/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

• Benefits are available in the member’s contract/certificate, and
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane (HAM) products (AmnioBand® Membrane, Biovance®, EpiCord®, Epifix®, Grafix™)‡ to be eligible for coverage.**

Based on review of available data, the Company may consider HAM grafts with or without suture (Prokera®, AmbioDisk™)‡ for the treatment of any of the following ophthalmic indications to be eligible for coverage:**

• Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see Policy Guidelines); or
• Corneal ulcers and melts that do not respond to initial conservative therapy (see Policy Guidelines); or
• Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment; or
• Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty); or
• Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient; or
• Moderate or severe Stevens-Johnson syndrome; or
• Persistent epithelial defects that do not respond to conservative therapy (See Policy Guidelines); or

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- Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or
- Moderate or severe acute ocular chemical burn.

Based on review of available data, the Company may consider human amniotic membrane grafts with suture or glue for the treatment of the following ophthalmic indications to be eligible for coverage:*

- Corneal perforation when corneal tissue is not immediately available; or
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

**When Services Are Considered Investigational**

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers injection of micronized or particulated human amniotic membrane for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis to be investigational.*

Based on review of available data, the Company considers human amniotic membrane grafts with or without suture for all ophthalmic indications not outlined above to be investigational.*

Based on review of available data, the Company considers injection of human amniotic fluid for all indications to be investigational.*

Based on review of available data, the Company considers all other human amniotic membrane (HAM) products and indications not listed above, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency, to be investigational.*

**Policy Guidelines**

Nonhealing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks, based on the entry criteria for clinical trials (eg, Zelen et al, 2015).
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Conservative therapy for neurotrophic keratitis may include 5 days of pressure patching, therapeutic contact lens, topical lubricants, and topical antibiotics.

Conservative therapy for corneal ulcers and melts may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents.

A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment of a persistent epithelial defect may include 5 days of the following: topical lubricants, topical antibiotics, therapeutic contact lens, or patching.

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)

Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:
- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
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- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

Step 4:
If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

**Dry eye severity level DEWS 3 to 4**
Discomfort, severity, and frequency - Severe frequent or constant
Visual symptoms - chronic and/or constant, limiting to disabling
Conjunctival Injection - +/- or ++/
Conjunctive Staining - moderate to marked
Corneal Staining - marked central or severe punctate erosions
Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris
Lid/meibomian glands - Frequent
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Tear film breakup time - < 5
Schirmer score (mm/5 min) - < 5

**Background/Overview**

**Human Amniotic Membrane**

HAM consists of two conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac or placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. Many products available using amnion, chorion, amniotic fluid, and umbilical cord are being studied for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions. The products are formulated either as patches, which can be applied as wound covers, or as suspensions or particulates, or connective tissue extractions, which can be injected or applied topically (see Table 1).

The fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. There is evidence the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures. Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.
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**Amniotic Fluid**

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea. The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.

**Table 1. Amniotic Membrane and Amniotic Fluid Preparations: Preparation and Components**

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
<td>C</td>
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</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
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<td></td>
</tr>
<tr>
<td>AmbioDry5® (IOP Ophthalmics)</td>
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<td></td>
</tr>
<tr>
<td>AmnioBand® Membrane (MTF Wound Care)</td>
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</tr>
<tr>
<td>AmnioClear™ (Liventa Bioscience)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmnioExcel® (Derma Sciences)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioFix® (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioGraft® (Bio-Tissue)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Artacent® Wound (Tides Medical)</td>
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<td>BioDDryFlex® (BioD)</td>
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<td>BioDfence™ (BioD)</td>
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<tr>
<td>BioSkin (HRT)</td>
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</table>

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<tr>
<th>Product (Supplier)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Biovance® (Alliqua Biomedical)</td>
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<tr>
<td>Clarix® (Amniox Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>Cygnus (Vivex Biomedical)</td>
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<tr>
<td>Cygnus Max (Vivex Biomedical)</td>
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<tr>
<td>EpiCord™ (MiMedx)</td>
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<tr>
<td>EpiFix® (MiMedx)</td>
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<td>X</td>
</tr>
<tr>
<td>Dermavest™ (Aedicell)</td>
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</tr>
<tr>
<td>Grafix® (Osiris)</td>
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<td>X</td>
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<tr>
<td>Guardian/AmnioBand® (MTF Wound Care)</td>
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<td>X</td>
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<tr>
<td>Neox® 100 (Amniox Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>Neox® Cord (Amniox Medical)</td>
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<td>Neox® Wound Allograft (Amniox Medical)</td>
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<tr>
<td>NuShield™ (NuTech Medical)</td>
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<td>PalinGen® Membrane (Amnio ReGen Solutions)</td>
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</tr>
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<td>Plurivest™ (Aedicell)</td>
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<tr>
<td>Prokera® (Bio-Tissue)</td>
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<tr>
<td>Revitalon™ (Medline Industries)</td>
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<td>X</td>
</tr>
<tr>
<td>WoundEx® (Skye Biologics)</td>
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<td>X</td>
</tr>
<tr>
<td>Suspension, particulate, or extraction</td>
<td></td>
<td></td>
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<tr>
<td>AmnioBand® Particulate (MTF Wound Care)</td>
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<td>X</td>
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<td>AmnioMatrix® (Derma Sciences)</td>
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<td>X</td>
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<td>AmnioVisc™ (Lattice Biologies)</td>
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<td>X</td>
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<tr>
<td>BioSkin® Flow (HRT)</td>
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<td>Clarix® Flo (Amniox Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>Interfyl™ (Alliqua Biomedical)</td>
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<td>X</td>
</tr>
<tr>
<td>Neox® Flo (Amniox Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>OrthoFlo™ (MiMedx)</td>
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<td>X</td>
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</tbody>
</table>
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</thead>
<tbody>
<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
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<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
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<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® Flow (Skye Biologics)b</td>
<td>E</td>
<td>X</td>
</tr>
</tbody>
</table>

C: cryopreserved; D: dehydrated; E: extracted connective tissue; HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation; NS: not specified.

a,b Processed by HRT and marketed by under different tradenames.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. HAM products and amniotic fluid products are included in these regulations.

In 2003, Prokera was cleared for marketing by the Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The Food and Drug Administration determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.” The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

AmnioClip (FORTECH GmbH) is a ring designed to hold the amniotic membrane in the eye without sutures or glue fixation. A mounting device is used to secure the amniotic membrane within the AmnioClip. The AmnioClip currently has CE approval in Europe.
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Rationale/Source
Several commercially available forms of human amniotic membrane (HAM) and amniotic fluid can be administered by patches, topical application, or injection. Amniotic membrane and amniotic fluid are being evaluated for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions.

Diabetic Lower-Extremity Ulcers
For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes randomized controlled trials (RCTs). The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life (QOL). The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Lower-Extremity Ulcers due to Venous Insufficiency
For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch or flowable formulation of HAM, the evidence includes two RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of lower-extremity venous ulcers includes two multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at four weeks, but the percentage of patients with complete wound closure did not differ between EpiFix and standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the
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standard of care for venous insufficiency ulcers are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Osteoarthritis**
For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. The pilot study assessed the feasibility of a larger RCT evaluating HAM injection. Additional trials, which will have a larger sample size and longer follow-up, are needed to permit conclusions on the effect of this treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Plantar Fasciitis**
The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (n=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in the Visual Analog Score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an interim report with 12-month results pending. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ophthalmic Conditions**
**Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy**
For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
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**Corneal Ulcers and Melts That Does Not Respond to Initial Medical Therapy**

For individuals who have corneal ulcers and melts that does not respond to initial medical therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment**

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Bullous Keratopathy as a Palliative Measure in Patients Who are not Candidates for a Curative Treatment (eg, endothelial or penetrating keratoplasty)**

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient**
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For individuals who have partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Moderate or Severe Stevens-Johnson Syndrome**

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of Stevens-Johnson includes one RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease, supported the use of HAM for moderate or severe Stevens-Johnson syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Persistent Epithelial Defects and Ulceration That Do Not Respond to Conservative Therapy**

For individuals who have persistent epithelial defects that do not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulcerations that do not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Severe Dry Eye with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy**

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case
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series. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns
For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is not Immediately Available
For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to
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create a conjunctival autograft (eg, extensive, double, or recurrent pterygium). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
2019
In response to requests while this policy was under review in 2018-2019, clinical input on the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

Practice Guidelines and Position Statements
Society for Vascular Surgery et al
The Society for Vascular Surgery (2016) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4. Table 13. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
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<td>NCT03441607a</td>
<td>Safety &amp; Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane)® in Adults With Pain Due to Osteoarthritis of the Knee</td>
<td>320</td>
<td>Mar 2019</td>
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<tr>
<td>NCT02318511a</td>
<td>An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis</td>
<td>200</td>
<td>Dec 2019</td>
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<td>NCT03414255a</td>
<td>A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial Of The Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Achilles Tendonitis</td>
<td>158</td>
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<td>NCT03414268a</td>
<td>A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Plantar Fasciitis</td>
<td>164</td>
<td>Oct 2019</td>
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<tr>
<td>NCT03379324a</td>
<td>A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft</td>
<td>260</td>
<td>Sep 2019</td>
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<tr>
<td>NCT02322554</td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
<td>50,000</td>
<td>Jan 2020</td>
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<tr>
<td>NCT03390920</td>
<td>Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions</td>
<td>200</td>
<td>Jun 2022</td>
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<td>Unpublished</td>
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Amniotic Membrane and Amniotic Fluid

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NCT02609594a A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers 240 Dec 2018

NCT02838784a The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study 134 Dec 2018

NCT02880592a A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Fresh Amniotic Membrane in the Treatment of Diabetic Foot Ulcers 100 Jan 2019

NCT No. | Trial Name | Planned Enrollment | Completion Date

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References

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33. Cazzell, SS, Stewart, JJ, Agnew, PP, Senatore, JJ, Walters, JJ, Murdoch, DD, Reyzelman, AA, Miller, SS. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. NA. PMID 30058377.

Policy History
Original Effective Date:  08/19/2015
Current Effective Date:  04/24/2019
08/06/2015 Medical Policy Committee review
08/19/2015 Medical Policy Implementation Committee approval. New policy.
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017 Medical Policy Committee review
Amniotic Membrane and Amniotic Fluid

Policy #  00458
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08/23/2017 Medical Policy Implementation Committee approval. AmnioBand Membrane, Biovance, Epifix, Grafix considered medically necessary for diabetic foot ulcers; all other products and indications are investigational. Sutured amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Ophthalmic products added and discontinued product names removed from Table 1.

05/03/2018 Medical Policy Committee review
05/16/2018 Medical Policy Implementation Committee approval. Investigational indications clarified.

04/04/2019 Medical Policy Committee review
04/24/2019 Medical Policy Implementation Committee approval. EpiCord add to medically necessary statement for diabetic lower extremity ulcers. Sutured and non-sutured amniotic membrane may be considered medically necessary for specified ophthalmic conditions.

Coding

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tr>
<td>CPT</td>
<td>15271, 15275, 17999, 65778, 65779</td>
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<td>HCPCS</td>
<td>Q4100, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4177, Q4178, Q4179, Q4181, V2790</td>
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<td>New codes added 1/1/19: Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4204</td>
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<td>Code deleted eff 1/1/19: Q4131</td>
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</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or  
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);  
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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