FEP Medical Policy Manual

FEP 7.01.149 Amniotic Membrane and Amniotic Fluid

Effective Policy Date: July 1, 2019
Original Policy Date: January 2017

Related Policies:
2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors for Healing and Other Non–Orthopedic Conditions
7.01.113 Bioengineered Skin and Soft Tissue Substitutes
8.01.52 Orthopedic Applications of Stem Cell Therapy

Amniotic Membrane and Amniotic Fluid

Description

OBJECTIVE

The objective of this evidence review is to evaluate whether various human amniotic membrane products improve the net health outcome for patients with various diabetic and venous ulcers, osteoarthritis, plantar fasciitis, and ophthalmic conditions.

POLICY STATEMENT

Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products (AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix™) may be considered medically necessary.

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Human amniotic membrane grafts with or without suture (Prokera, AmbioDisk™) may be considered medically necessary for the treatment of the following ophthalmic indications:

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

Human amniotic membrane grafts with suture or glue may be considered medically necessary for the treatment of the following ophthalmic indications:

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

Human amniotic membrane grafts with or without suture are considered investigational for all ophthalmic indications not outlined above.

Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis.

Injection of human amniotic fluid is considered investigational for all indications.

All other human amniotic membrane products and indications not listed above are considered investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency.

**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 (e.g., Zelen et al, 2015).

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:

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• 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
• 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

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Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., 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 +/-
Conjunctival 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
Tear film breakup time - < 5
Schirmer score (mm/5 min) - < 5

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

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

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cryopreserved,</td>
<td>Amnion Chorion</td>
</tr>
<tr>
<td></td>
<td>Dehydrated, or</td>
<td>Amniotic Fluid</td>
</tr>
<tr>
<td></td>
<td>Extracted</td>
<td>Umbilical Cord</td>
</tr>
<tr>
<td>Patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>AmbioDry5® (IOP Ophthalmics)</td>
<td>D</td>
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</tbody>
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<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
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<tbody>
<tr>
<td>Neox® Wound Allograft (Amniox Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>NuShield™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>PalinGen® Membrane (Amnio ReGen Solutions)</td>
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<td>X</td>
</tr>
<tr>
<td>Plurivest™ (Aedicell)</td>
<td>C</td>
<td>X</td>
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<tr>
<td>Prokera® (Bio-Tissue)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Revitalon™ (Medline Industries)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® (Skye Biologics)</td>
<td>D</td>
<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>
<td>D</td>
<td>X</td>
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<tr>
<td>AmnioMatrix® (Derma Sciences)</td>
<td>D</td>
<td>X</td>
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<tr>
<td>AmnioVisc™ (Lattice Biologics)</td>
<td>NS</td>
<td>X</td>
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<tr>
<td>BioSkin® Flow (HRT)</td>
<td>E</td>
<td>X</td>
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<td>Clarix® Flo (Amniox Medical)</td>
<td>C</td>
<td>X</td>
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<tr>
<td>Interfy™ (Alliqua Biomedical)</td>
<td>NS</td>
<td>X</td>
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<tr>
<td>Neox® Flo (Amniox Medical)</td>
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<tr>
<td>OrthoFlo™ (MiMedx)</td>
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<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
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<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
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<td>X</td>
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<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
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<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D</td>
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### RATIONALE

#### Summary of Evidence

**Diabetic Lower-Extremity Ulcers**

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (i.e., AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and 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 ITT analysis. For the HAM products that have been sufficiently evaluated (i.e., 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 HAM products 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 the SOC. 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 SOC 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...

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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**

For individuals who have plantar fasciitis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes two small RCTs. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Research on HAM injections for plantar fasciitis is at an early stage. The evidence includes a small (n=23) double-blind comparison with corticosteroid and a patient-blinded (n=45) comparison of 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of HAM and amniotic fluid injections on plantar fasciitis pain. 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 and 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.

**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.

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Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient

For individuals who have partial LSCD 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 LSCD. 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. 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 does not Respond to Conservative Therapy

For individuals who have persistent epithelial defects that does 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 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.

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 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

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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 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**

**Practice Guidelines and Position Statements**

**Tear Film and Ocular Surface Society**

The Tear Film and Ocular Surface Society (2017) published the DEWS [Dry Eye Workshop] II management and therapy report. The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

**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
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease

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• 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)

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."^33, 33

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.

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REFERENCES


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32. 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.


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<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2017</td>
<td>New Policy</td>
<td>Policy updated with literature review through November 7, 2016; material on patch formulations of amniotic membrane moved from policy 7.01.113 (Bioengineered Skin and Soft Tissue Substitutes); references 7-8, 15, 18, 20, and 22-23 added. AmnioBand®, Biovance®, Epifix®, Grafix™ considered medically necessary for diabetic foot ulcers; all other products and indications are investigational.</td>
</tr>
<tr>
<td>March 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 27, 2017; references 21-28 added. Clinical input reviewed. Fixed amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens Johnson, and persistent epithelial defects.</td>
</tr>
<tr>
<td>June 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 11, 2017; references 15, 22, and 27 added. Specific indications added to the investigational policy statements.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 27, 2018; references added. Clinical input reviewed. 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.</td>
</tr>
</tbody>
</table>

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