Amniotic Membrane and Amniotic Fluid

Description

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.

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.

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;

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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 products not listed above are considered investigational (see policy guidelines).

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

**POLICY GUIDELINES**

Non-healing 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]).

Tables PG1 and PG2 list the medically necessary and investigational amniotic products that have an HCPCS code.

**Table PG1 Amniotic Products Listed in the Policy Statements**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Supplier</th>
<th>HCPCS Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmnioBand Membrane</td>
<td>MTF Wound Care</td>
<td>Q4151</td>
</tr>
<tr>
<td>Biovance</td>
<td>Celularity</td>
<td>Q4154</td>
</tr>
</tbody>
</table>

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### Table PG2 Other Amniotic Products with HCPCS Codes

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Supplier</th>
<th>HCPCS Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity™</td>
<td>NuTech Medical</td>
<td>Q4159</td>
</tr>
<tr>
<td>Allogen</td>
<td>Vivex Biomedical</td>
<td>Q4212</td>
</tr>
<tr>
<td>AlloWrap™</td>
<td>AlloSource</td>
<td>Q4150</td>
</tr>
<tr>
<td>Amnioarmor™</td>
<td>Tissue Transplant Technology</td>
<td>Q4188</td>
</tr>
<tr>
<td>AmnioBand Particulate</td>
<td>MTF Wound Care</td>
<td>Q4168</td>
</tr>
<tr>
<td>AmnioExcel</td>
<td>Derma Sciences</td>
<td>Q4137</td>
</tr>
<tr>
<td>Amnion bio or Axomembrane</td>
<td>Axolotl Biologix</td>
<td>Q4211</td>
</tr>
<tr>
<td>AmnioMatrix</td>
<td>Integra Life Sciences</td>
<td>Q4139</td>
</tr>
<tr>
<td>AmnioWrap2™</td>
<td>Direct Biologics</td>
<td>Q4221</td>
</tr>
<tr>
<td>Articent ac (flowable)</td>
<td>Tides Medical</td>
<td>Q4189</td>
</tr>
<tr>
<td>Artacent ac (patch)</td>
<td>Tides Medical</td>
<td>Q4190</td>
</tr>
<tr>
<td>Artacent Wound</td>
<td>Tides Medical</td>
<td>Q4169</td>
</tr>
<tr>
<td>Artacent Cord</td>
<td>Tides Medical</td>
<td>Q4126</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascent</td>
<td>StimLabs</td>
<td>Q4213</td>
</tr>
<tr>
<td>Axolotl ambien or Axolotl Cryo</td>
<td>Axolotl Biology</td>
<td>Q4215</td>
</tr>
<tr>
<td>BioDDryFlex</td>
<td>BioD</td>
<td>Q4138</td>
</tr>
<tr>
<td>BioDfence™</td>
<td>Integra Life Science</td>
<td>Q4140</td>
</tr>
<tr>
<td>BioWound, BioWound Plus™, BioWound XPlus™</td>
<td>HRT®</td>
<td>Q4217</td>
</tr>
<tr>
<td>Cellesta/Cellesta duo</td>
<td>Ventris Medical</td>
<td>Q4184</td>
</tr>
<tr>
<td>Cellesta Cord</td>
<td>Ventris Medical</td>
<td>Q4214</td>
</tr>
<tr>
<td>Cellesta flowable</td>
<td>Ventris Medical</td>
<td>Q4185</td>
</tr>
<tr>
<td>Clarix</td>
<td>Amniox Medical</td>
<td>Q4156</td>
</tr>
<tr>
<td>Clarix Flo</td>
<td>Amniox Medical</td>
<td>Q4155</td>
</tr>
<tr>
<td>Cygnus</td>
<td>Vivex Biomedical</td>
<td>Q4170</td>
</tr>
<tr>
<td>Dermavest™ or Plurivest</td>
<td>AediCell®</td>
<td>Q4153</td>
</tr>
<tr>
<td>Epifix Injectable</td>
<td>MiMedx</td>
<td>Q4145</td>
</tr>
<tr>
<td>Fluid flow or Fluid GF</td>
<td>BioLab Sciences</td>
<td>Q4206</td>
</tr>
<tr>
<td>Genesis</td>
<td>Genesis Biologics</td>
<td>Q4198</td>
</tr>
<tr>
<td>Guardian/AmnioBand</td>
<td>MTF Wound Care</td>
<td>Q4151</td>
</tr>
<tr>
<td>Matrion</td>
<td>LifeNet Health</td>
<td>Q4201</td>
</tr>
<tr>
<td>Neox Cord</td>
<td>Amniox Medical</td>
<td>Q4148</td>
</tr>
<tr>
<td>Neox Flo</td>
<td>Amniox Medical</td>
<td>Q4155</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neox Wound</td>
<td>Amniox Medical</td>
<td>Q4156</td>
</tr>
<tr>
<td>Novachor</td>
<td>Organogenisis</td>
<td>Q4191</td>
</tr>
<tr>
<td>Novafix</td>
<td>Triad Life Sciences</td>
<td>Q4208</td>
</tr>
<tr>
<td>NuShield</td>
<td>Organogenesis</td>
<td>Q4160</td>
</tr>
<tr>
<td>PalinGen Membrane</td>
<td>Amnio ReGen Solutions</td>
<td>Q4173</td>
</tr>
<tr>
<td>PalinGen SportFlow</td>
<td>Amnio ReGen Solutions</td>
<td>Q4174</td>
</tr>
<tr>
<td>Plurivest™</td>
<td>AediCell</td>
<td>Q4153</td>
</tr>
<tr>
<td>Restorigin</td>
<td>UMTB Biomedical</td>
<td>Q4191</td>
</tr>
<tr>
<td>Restorigin Injectable</td>
<td>UMTB Biomedical</td>
<td>Q4192</td>
</tr>
<tr>
<td>Revitalon™</td>
<td>Medline Industries</td>
<td>Q4157</td>
</tr>
<tr>
<td>Surgicord</td>
<td>Synergy Biologics</td>
<td>Q4218</td>
</tr>
<tr>
<td>SurgiGRAFT™</td>
<td>Synergy Biologics</td>
<td>Q4183</td>
</tr>
<tr>
<td>WoundEx</td>
<td>Skye Biologics^a</td>
<td>Q4163</td>
</tr>
<tr>
<td>WoundEx Flow</td>
<td>Skye Biologics^a</td>
<td>Q4162</td>
</tr>
<tr>
<td>Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)</td>
<td>HRT</td>
<td>Q4217</td>
</tr>
<tr>
<td>Xwrap</td>
<td>Applied Biologics</td>
<td>Q4204</td>
</tr>
</tbody>
</table>

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation

^a Processed by HRT and marketed under different tradename

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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
- 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

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- 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 disablign
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
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**

The U.S. Food and Drug Administration (FDA) 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. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[^1]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

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1. "The HCT/P is minimally manipulated;

2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4. Either:
   1. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
   2. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
      1. Is for autologous use;
      2. Is for allogeneic use in a first-degree or second-degree blood relative; or
      3. Is for reproductive use."

The guidance provides the following specific examples of homologous and non-homologous use for amniotic membrane:

1. "Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.

2. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.

3. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane."

The FDA noted the intention to exercise enforcement discretion for the next 36 months after publication of the guidance.

In 2003, Prokera™ was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The FDA 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.

**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 or placental membrane (ie, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes...
randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for venous insufficiency ulcers. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy for this indication. 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. Relevant outcomes are symptoms, functional outcomes, quality of life, 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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

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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 (SJS) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of SJS includes 1 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 SJS. 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

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For individuals who have persistent epithelial defects that do not respond to conservative therapy who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no 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.

**Moderate or Severe Acute Ocular Chemical Burns**

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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**

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Tear Film and Ocular Surface Society

In 2017, the Tear Film and Ocular Surface Society published the Dry Eye Workshop II (DEWS) 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
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-gluocorticoid 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

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- 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 (e.g., tarsorrhapy, salivary gland transplantation)

**Society for Vascular Surgery et al.**

In 2016, the Society for Vascular Surgery 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, amnionic 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.

**REFERENCES**

6. Ananian, CC, Dhillon, YY, Van Gils, CC, Lindsey, DD, Otto, RR, Dove, CC, Pierce, JJ, Saunders, MM. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-


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


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<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 Membrane, Biovance, Epifix, Grafix™ considered medically necessary for diabetic foot ulcers; all other products and indications are investigational.</td>
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<tr>
<td>March 2017</td>
<td>Replace policy</td>
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<tr>
<td>June 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 27, 2017; references 21-28 added. Clinical input reviewed. Fixated 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>March 2018</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>June 2019</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>
<tr>
<td>June 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 20, 2019; references added. Policy statements unchanged.</td>
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