Introduction

The amniotic membrane and amniotic fluid are structures that surround the fetus in the uterus (womb). The fluid protects the fetus from injury. The membrane is a thin mesh of protein and contains growth factors, stem cells, and other items crucial to a developing fetus. Processing and then using the amniotic membrane and/or fluid (after delivery), has been proposed to treat a number of conditions in adults. High quality medical studies show that using specific amniotic membrane products may be useful for treating diabetic ulcers in some cases, for specific eye conditions, and for a disorder known as Stevens-Johnson syndrome. This policy describes when these products may be considered medically necessary. Using amniotic membrane for other conditions or using amniotic fluid products is considered unproven (investigational).

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Treatment of nonhealing diabetic lower-extremity ulcers | Treatment of nonhealing* diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary:  
  - Affinity®  
  - AmnioBand® Membrane  
  - Biovance®  
  - EpiCord®  
  - Epifix®  
  - Grafix®  
  
  *Note: Nonhealing 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).  
  
  When the above medical necessity criteria are met, the following conditions of coverage will apply:  
  - Treatment is limited to a maximum of 6 applications in 12 weeks when evidence of wound healing is present  
  
  Graft applications that exceed what is reasonable and necessary as size-appropriate based on the size of the wound are considered not medically necessary (see Related Information).  
  
  Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status. |
### Service | Medical Necessity
---|---
- Corneal ulcers and melts that do not respond to initial conservative therapy (see *Definition of Terms*).
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Moderate or severe acute ocular chemical burn.
- Moderate or severe Stevens-Johnson syndrome.
- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see *Definition of Terms*).
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Persistent epithelial defects that do not respond to conservative therapy (see *Definition of Terms*).
- 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 *Related Information*).

**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.

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human amniotic membrane for other ophthalmic indications</strong></td>
<td><strong>Human amniotic membrane grafts with or without suture are considered investigational for all ophthalmic indications not outlined above.</strong></td>
</tr>
</tbody>
</table>
| **Injection of micronized or particulated human amniotic membrane** | **Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of:**
  - osteoarthritis
  - plantar fasciitis |
Injection of human amniotic fluid is considered investigational for all indications.

Other indications

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

Investigational

All other human amniotic membrane products not listed above are considered investigational, including but not limited to:

- AlloGen® liquid
- AlloWrap® DS or dry
- AltiPly™
- AmnioAMP-MP™
- AmnioArmor™
- AmnioBand® Particulate
- Amniocore™
- Amniocyte™
- Amniocyte plus™
- Amnioexcel®
- Amnioexcel® plus
- Amnio-maxx™
- AmnioMatrix® injectable
- Amnion Bio
- Amniorepair®
- Amniotext®
- Amniotext patch
- Amnio Wound
- Amnio Wrap2™
- Amniply®
- Artacent® AC (flowable)
- Artacent® AC (patch)
- Artacent® Cord
- Artacent® Wound
- Ascent
- Axobiomembrane
- Axolotl Ambient®
- Axolotl Cryo®
- Axolotl DualGraft™
- carePATCH
- Cellesta™
- Cellesta™ Cord
- Cellesta™ Duo
- Cellesta™ flowable amnion injectable
- Clarix 100
- Clarix® Cord 1K
- ClarixFlo®
- Cogenex flowable amnion
- Cogenex amniotic membrane
- Corecyte™
- Corplex
- Coreplex P
- Coretext™
- Cryo-cord™
- Cygnus™
- Dermacyte®
- Dermavest®
- Derm-maxx
- Epifix Injectable
- FlowerAmnioFlo® (liquid)
- FlowerAmnioPatch
- Fluid Flow™ liquid
- Fluid GF liquid
- Genesis amniotic membrane
- Interfyl®
- Kerox®
- Matrion
- Membrane Graft
- Novachor™
- Novafix®
- Novafix® DL
- Nudyn®
- NuShield®
- PalinGen® Membrane
- PalinGen® XPlus
- PalinGen® SportFlow
- Plurivest™
- ProMatrx liquid
- Polycyte™
- Procenta®
- Protext™
- Reguard
- Restorigin™
- Restorigin™ Injectable
- Revita®
- Revitalon™
- Surfator®
- Surgenex,
- SurgicORD
- SurgiGraft®
- SurgiGRAFT™
- SurgiGRAFT™-DUAL
- Therion
- WoundEx®
- WoundEx® Flow
- WoundFix™
- WoundFix™ Plus
- WoundFix™ Xplus
Axolotl Graft™
Biodexcel
BioDFence®
BioDFence® DryFlex®
BioDMatrix injectable
BioNext® PATCH
BioSkin®
BioSkin® Flow
BioWound™
BioWound™ Plus
BioWound™ Xplus
Membrane Wrap
Neopatch®
Neox® 100
Neox™ Cord 1k
Neox® Cord-RT
Neox® Flo
Neox® Wound
Xcellerate™
Xwrap®

Note:  HRT: Human Regenerative Technologies; MTF Musculoskeletal Transplant Foundation ® Processed by HRT and marketed under different tradename

Documentation Requirements

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Name of product to be used
- Previous therapy attempted and for how long

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4132</td>
<td>Grafix Core and GrafixPL Core, per sq cm</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter</td>
</tr>
<tr>
<td>Q4145</td>
<td>EpiFix®, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4151</td>
<td>AmnioBand® or Guardian, per sq cm</td>
</tr>
<tr>
<td>Q4154</td>
<td>Biovance®, per sq cm</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity®, per sq cm</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4168</td>
<td>AmnioBand®, 1 mg</td>
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<tr>
<td>Q4186</td>
<td>Epifix®, per square centimeter</td>
</tr>
<tr>
<td>Q4187</td>
<td>EpiCord®, per square centimeter</td>
</tr>
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</table>

**Investigational (Not Eligible for Coverage)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified)</td>
</tr>
<tr>
<td>Q4137</td>
<td>AmnioExcel®, AmnioExcel® Plus or Biodexcel, per sq cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>BioDFence® DryFlex, per sq cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix® or BioDMatrix, injectable, 1 cc.</td>
</tr>
<tr>
<td>Q4140</td>
<td>BioDFence®, per sq cm</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox™ Cord 1k, Neox® Cord RT, or Clarix® Cord 1K, per sq cm</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap® DS or dry, per square centimeter</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest® and Plurivest™, per sq cm</td>
</tr>
<tr>
<td>Q4155</td>
<td>Neox® Flo or Clarix Flo®, 1 mg</td>
</tr>
<tr>
<td>Q4156</td>
<td>Neox® 100 or Clarix 100, per sq cm</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon™, per sq cm</td>
</tr>
<tr>
<td>Q4160</td>
<td>Nushield®, per sq cm</td>
</tr>
<tr>
<td>Q4162</td>
<td>WoundEx® Flow, BioSkin® Flow, 0.5 cc</td>
</tr>
<tr>
<td>Q4163</td>
<td>WoundEx®, BioSkin®, per sq cm</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent® wound, per sq cm</td>
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<tr>
<td>Q4170</td>
<td>Cygnus™ per sq cm</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl®, 1 mg</td>
</tr>
<tr>
<td>Q4173</td>
<td>PalinGen® or PalinGen® XPlus, per sq cm</td>
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<tr>
<td>Q4174</td>
<td>PalinGen® or ProMatrX, 0.36 mg per 0.25 cc</td>
</tr>
<tr>
<td>Q4176</td>
<td>Neopatch or therion, per square centimeter</td>
</tr>
<tr>
<td>Q4177</td>
<td>FlowerAmnioFlo®, 0.1 cc</td>
</tr>
<tr>
<td>Q4178</td>
<td>FlowerAmnioPatch, per sq cm</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4180</td>
<td>Revita®, per sq cm</td>
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<tr>
<td>Q4181</td>
<td>Amnio Wound, per sq cm</td>
</tr>
<tr>
<td>Q4183</td>
<td>SurgiGRAFT™, per square centimeter</td>
</tr>
<tr>
<td>Q4184</td>
<td>Cellesta™ or Cellesta™ Duo, per square centimeter</td>
</tr>
<tr>
<td>Q4185</td>
<td>Cellesta™ flowable amnion (25 mg per cc); per 0.5 cc</td>
</tr>
<tr>
<td>Q4188</td>
<td>AmnioArmor™, per square centimeter</td>
</tr>
<tr>
<td>Q4189</td>
<td>Artacent® AC, 1 mg</td>
</tr>
<tr>
<td>Q4190</td>
<td>Artacent® AC, per square centimeter</td>
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<tr>
<td>Q4191</td>
<td>Restorigin™, per square centimeter</td>
</tr>
<tr>
<td>Q4192</td>
<td>Restorigin™, 1 cc</td>
</tr>
<tr>
<td>Q4194</td>
<td>Novachor™, per square centimeter</td>
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<tr>
<td>Q4198</td>
<td>Genesis Amniotic Membrane, per square centimeter</td>
</tr>
<tr>
<td>Q4201</td>
<td>Matrion, per sq cm</td>
</tr>
<tr>
<td>Q4202</td>
<td>Keroxx ® (2.5 g/cc), 1 cc</td>
</tr>
<tr>
<td>Q4204</td>
<td>XWRAP, per square centimeter</td>
</tr>
<tr>
<td>Q4205</td>
<td>Membrane Graft or Membrane Wrap, per sq cm</td>
</tr>
<tr>
<td>Q4206</td>
<td>Fluid Flow™ or Fluid GF, 1 cc</td>
</tr>
<tr>
<td>Q4208</td>
<td>Novafix®, per sq cm</td>
</tr>
<tr>
<td>Q4209</td>
<td>SurGraft®, per sq cm</td>
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<tr>
<td>Q4210</td>
<td>Axolotl Graft® or Axolotl DualGraft®, per sq cm</td>
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<tr>
<td>Q4211</td>
<td>Amnion Bio or AxoBioMembrane, per sq cm</td>
</tr>
<tr>
<td>Q4212</td>
<td>AlloGen®, per cc</td>
</tr>
<tr>
<td>Q4213</td>
<td>Ascent, 0.5 mg</td>
</tr>
<tr>
<td>Q4214</td>
<td>Cellesta Cord™, per sq cm</td>
</tr>
<tr>
<td>Q4215</td>
<td>Axolotl Ambient® or Axolotl Cryo®, 0.1 mg</td>
</tr>
<tr>
<td>Q4216</td>
<td>Artacent® Cord, per sq cm</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4217</td>
<td>WoundFix™, BioWound™, WoundFix™ Plus, BioWound™ Plus, WoundFix™ Xplus or</td>
</tr>
<tr>
<td></td>
<td>BioWound™ Xplus, per sq cm</td>
</tr>
<tr>
<td>Q4218</td>
<td>SurgiCORD, per sq cm</td>
</tr>
<tr>
<td>Q4219</td>
<td>SurgiGRAFT™-DUAL, per sq cm</td>
</tr>
<tr>
<td>Q4221</td>
<td>Amnio Wrap2™, per sq cm</td>
</tr>
<tr>
<td>Q4227</td>
<td>AmnioCore™ per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4228</td>
<td>BioNext® PATCH, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4229</td>
<td>Cogenex Amniotic Membrane, per sq cm (new code effective 7/1/20)</td>
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<tr>
<td>Q4230</td>
<td>Cogenex Flowable Amnion, per 0.5 cc (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4231</td>
<td>Corplex P, per cc (new code effective 7/1/20)</td>
</tr>
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<td>Q4232</td>
<td>Corplex, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4233</td>
<td>SurFactor® or NuDyn®, per 0.5 cc (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4234</td>
<td>XCellerate™, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4235</td>
<td>AMNIOREPAIR® or AltiPly™, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4236</td>
<td>carePATCH, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4237</td>
<td>Cryo-Cord™, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4239</td>
<td>Amnio-Maxx™ or Amnio-Maxx™ Lite, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4240</td>
<td>CoreCyte™, for topical use only, per 0.5 cc (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4241</td>
<td>PolyCyte™, for topical use only, per 0.5 cc (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4242</td>
<td>AmnioCyte Plus™, per 0.5 cc (new code effective 7/1/20)</td>
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<td>Q4244</td>
<td>Procenta®, per 200 mg (new code effective 7/1/20)</td>
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<tr>
<td>Q4245</td>
<td>AmnioText®, per cc (new code effective 7/1/20)</td>
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<tr>
<td>Q4246</td>
<td>CoreText™ or ProText™, per cc (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4247</td>
<td>Amniotext patch, per sq cm (new code effective 7/1/20)</td>
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<tr>
<td>Q4248</td>
<td>Dermacyte® Amniotic Membrane Allograft, per sq cm (new code effective 7/1/20)</td>
</tr>
<tr>
<td>Q4249</td>
<td>MNIPLY®, for topical use only, per square centimeter (new code effective 10/1/20)</td>
</tr>
<tr>
<td>Q4250</td>
<td>AmnioAmp-MPMP™, per square centimeter (new code effective 10/1/20)</td>
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<tr>
<td>Q4254</td>
<td>Novafix® DL, per square centimeter (new code effective 10/1/20)</td>
</tr>
<tr>
<td>Q4255</td>
<td>REGUaRD, for topical use only, per square centimeter (new code effective 10/1/20)</td>
</tr>
</tbody>
</table>

**Related Information**

**Definition of Terms**

**Persistent epithelial defect:** A defect 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.

**Conservative treatment:** The use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to human amniotic membrane grafts. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regarding treatments requiring multiple drops per day.

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.

**Tear Film Break-up Time (TFBUT):** The interval between the last complete blink and the first appearance of a dry spot, or disruption in the tear film after fluorescein has been instilled onto the bulbar conjunctiva and observed with a slit-lamp with the person staring straight ahead without blinking. A stop watch is used to record the time between the last complete blink and the first appearance of a dry spot in the tear film. Less than 5 seconds indicates a dry eye; greater than 5 seconds is considered normal.

**Schirmer’s Test:** Filter paper is placed inside the lower eyelid of both eyes and the person then closes their eyes for 5 minutes. Afterwards, the filter paper is assessed to see how far the tears have travelled on the paper. A measurement of less than 5 mm is considered a severely dry eye.
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
  - 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., tarsorrhaphy, salivary gland transplantation)

**Table 1. Dry Eye Severity Level Dry Eye Workshop Score (DEWS) 3 to 4**

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort, severity &amp; frequency</td>
<td>Severe frequent or constant without stress</td>
<td>Severe and/or disabling and constant</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>Annoying, chronic and/or constant, limiting activity</td>
<td>Constant and/or possibly disabling</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>+ / -</td>
<td>+ / ++</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Corneal staining (severity/location)</td>
<td>Marked central</td>
<td>Severe punctate erosions</td>
</tr>
</tbody>
</table>
Dry Eye Severity Level | 3 | 4
---|---|---
**Corneal/tear signs** | Filamentary keratitis, mucus clumping, increasing tear debris | Filamentary keratitis, mucus clumping, increasing tear debris, ulceration
**Lid/meibomian glands** | Frequent | Trichiasis, keratinization, symblepharon
**TFBUT (tear film break up test) (sec)** | ≤5 | Immediate
**Schirmer score (mm/5 min)** | ≤5 | ≤2


**Epifix® Sizing Guidelines**

The allograft is intended for single-patient use only. All unused material should be discarded. Multiple sizes are available in a wide range of sheet and mesh configurations covering wounds. To determine the measure of a wound in square centimeters multiply the length of the wound by the width of the wound in centimeters. (e.g., 10 cm in length x 5 cm in width = 50 cm²)

Here is a sample of the package standard sizes for Epifix:

### Table 2. Epifix® Sample of Package Standard Sizes

<table>
<thead>
<tr>
<th>Item Number</th>
<th>Size &amp; Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-5024</td>
<td>24 mm disk</td>
</tr>
<tr>
<td>GS-5330</td>
<td>3 cm x 3 cm sheet (9 sq cm)</td>
</tr>
<tr>
<td>GS-5350</td>
<td>3 cm x 5 cm sheet (15 sq cm)</td>
</tr>
<tr>
<td>GS-5460</td>
<td>4 cm x 6 cm sheet (24 sq cm)</td>
</tr>
<tr>
<td>GS-5560</td>
<td>5 cm x 6 cm sheet (30 sq cm)</td>
</tr>
<tr>
<td>GS-5770</td>
<td>7 cm x 7 cm sheet (49 sq cm)</td>
</tr>
<tr>
<td>ES-3500</td>
<td>3 cm x 5 cm mesh sheet (15 sq cm)</td>
</tr>
<tr>
<td>ES-4400</td>
<td>4 cm x 4.5 cm mesh sheet (18 sq cm)</td>
</tr>
<tr>
<td>ES-5500</td>
<td>5 cm x 5.5 cm mesh sheet (27.5 sq cm)</td>
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</tbody>
</table>

Table 3. AmnioBand® Sizing Guidelines

<table>
<thead>
<tr>
<th>Tissue Code</th>
<th>Product Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC3010</td>
<td>AmnioBand Membrane, 10mm Disk</td>
</tr>
<tr>
<td>WC3014</td>
<td>AmnioBand Membrane, 14mm Disk</td>
</tr>
<tr>
<td>WC3016</td>
<td>AmnioBand Membrane, 16mm Disk</td>
</tr>
<tr>
<td>WC3018</td>
<td>AmnioBand Membrane, 18mm Disk</td>
</tr>
<tr>
<td>WC3022</td>
<td>AmnioBand Membrane, 2cm x 2cm</td>
</tr>
<tr>
<td>WC3023</td>
<td>AmnioBand Membrane, 2cm x 3cm</td>
</tr>
<tr>
<td>WC3024</td>
<td>AmnioBand Membrane, 2cm x 4cm</td>
</tr>
<tr>
<td>WC3034</td>
<td>AmnioBand Membrane, 3cm x 4cm</td>
</tr>
<tr>
<td>WC3044</td>
<td>AmnioBand Membrane, 4cm x 4cm</td>
</tr>
<tr>
<td>WC3038</td>
<td>AmnioBand Membrane, 3cm x 8cm</td>
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<tr>
<td>WC3046</td>
<td>AmnioBand Membrane, 4cm x 6cm</td>
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<tr>
<td>WC3056</td>
<td>AmnioBand Membrane, 5cm x 6cm</td>
</tr>
<tr>
<td>WC3077</td>
<td>AmnioBand Membrane, 7cm x 7cm</td>
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</tbody>
</table>


Table 4. Other Product Size Specifications

<table>
<thead>
<tr>
<th>Name</th>
<th>Available Sizes</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>1.5 x 1.5 cm (2.25 square cm)</td>
<td><a href="https://affinityfresh.com/why-choose-affinity/product-details-and-resources.html">https://affinityfresh.com/why-choose-affinity/product-details-and-resources.html</a></td>
</tr>
<tr>
<td></td>
<td>2.5 x 2.5 cm (6.25 square cm)</td>
<td></td>
</tr>
<tr>
<td>Biovance®</td>
<td>1 x 2 cm</td>
<td><a href="https://www.biovance.net/ordering-information.html">https://www.biovance.net/ordering-information.html</a></td>
</tr>
<tr>
<td></td>
<td>2 x 2 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 x 3 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 x 4 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 x 3.5 cm</td>
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</tr>
<tr>
<td></td>
<td>4 x 4 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 x 5 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 x 6 cm</td>
<td></td>
</tr>
<tr>
<td>Epicord®</td>
<td>2 cm x 3 cm (6 sq cm)</td>
<td><a href="https://mimedx.com/epicord/">https://mimedx.com/epicord/</a> (see product details, other information)</td>
</tr>
<tr>
<td></td>
<td>3 cm x 5 cm (15 sq cm)</td>
<td></td>
</tr>
<tr>
<td>Grafix®</td>
<td>16 mm</td>
<td><a href="http://www.osiris.com/grafix/healthcare-professionals/">http://www.osiris.com/grafix/healthcare-professionals/</a></td>
</tr>
<tr>
<td></td>
<td>1.5 cm x 2 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 cm x 3 cm</td>
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</tbody>
</table>
### Evidence Review

#### 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.

#### Background

**Human Amniotic Membrane**

Human amniotic membrane (HAM) consists of 2 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 5).

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 that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered to be non-immunogenic and has not been observed to cause substantial immune response. It is believed that these properties are retained in cryopreserved HAM (C-HAM) and dehydrated HAM (D-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.²

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.¹ 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.

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.¹ 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 1927.³ 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.¹ Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. The use of stem cells in orthopedic applications is addressed in a separate policy (see Related Medical Policies).

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, Affinity, 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. The RCTs evaluating amniotic and placental membrane products for the treatment of nonhealing (<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 (ITT) analysis. For the HAM products that have been sufficiently evaluated (ie, Affinity, 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 quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes two 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 four 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 the 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 that the technology results in an improvement in the net health outcome.

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, 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 that the technology results in an improvement in the net health outcome.

**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 that the technology results in the net health outcome.

**Ophthalmic Conditions**

Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

**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 quality of life. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see **Clinical Input** below)

**Corneal Ulcers and Melts that Does Not Respond to Initial Medical Therapy**

For individuals who have corneal ulcers and melts that do not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-
randomized comparative study. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The systematic review showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in an 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 quality of life. No comparative evidence was identified for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)

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 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)

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 (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 quality of life. No
comparative trials 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)

**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. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome includes one RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease, thus supporting the use of HAM for moderate or severe Stevens-Johnson. The evidence is sufficient to determine that the technology results in an 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 do not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on persistent epithelial defects and ulceration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)

**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 do 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 quality of life. 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 three months. The evidence is
sufficient to determine that the technology results in an 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 three RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes an RCT of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the three RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)

**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 quality of life. The standard treatment for corneal perforation is corneal transplantation, however, HAM may provide temporary coverage of the severe defect 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 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see Clinical Input below)
Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT03414268</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>276</td>
<td>Apr 2021</td>
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<tr>
<td>NCT02982226</td>
<td>A Comparative Study of Injectable Human Amniotic Allograft (ReNu™) Versus Corticosteroids for Plantar Fasciitis: A Prospective, Randomized, Blinded Study</td>
<td>150</td>
<td>Apr 2021</td>
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<tr>
<td>NCT03414255</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>
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<td>May 2021</td>
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<tr>
<td>NCT03485157</td>
<td>A Phase 2B, Prospective, Double-blind, Randomized Controlled Trial of the Micronized Dehydrated Human Amnion Chorion Membrane Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee</td>
<td>466</td>
<td>Oct 2021</td>
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<tr>
<td>NCT04457752</td>
<td>A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers</td>
<td>124</td>
<td>Dec 2021</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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<tr>
<td>NCT04612023</td>
<td>A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee</td>
<td>90</td>
<td>Jul 2022</td>
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<tr>
<td>NCT04553432</td>
<td>Dry Eye OmniLenz Application of Omnigen Research Study</td>
<td>70</td>
<td>Jul 2022</td>
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<tr>
<td>NCT04599673</td>
<td>Prospective Analysis of Intraoperative AMNOGEN® Injection in Patients With Rotator Cuff Tear</td>
<td>100</td>
<td>Sep 2022</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT04636229*</td>
<td>A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee</td>
<td>474</td>
<td>Dec 2023</td>
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<tr>
<td>NCT03864939</td>
<td>Randomized Pilot Study to Improve Postprostatectomy Incontinence and Potency by Application of Dried Human Amnion Graft</td>
<td>328</td>
<td>Apr 2025</td>
</tr>
<tr>
<td>Unpublished</td>
<td>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</td>
<td>240</td>
<td>Dec 2018 (status unknown)</td>
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<tr>
<td>NCT02838784*</td>
<td>The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study</td>
<td>134</td>
<td>Dec 2018 (status unknown)</td>
</tr>
<tr>
<td>NCT03441607*</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 (status unknown)</td>
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<td>NCT02318511*</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>Feb 2019 (completed)</td>
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<tr>
<td>NCT03379324*</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 (status unknown)</td>
</tr>
</tbody>
</table>

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

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
2019 Input

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 Summary of Evidence section.

Clinical input was sought to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input 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.

Clinical input supported the use of amniotic membrane in individuals with the following indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.

- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.

- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.

- Bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) as an alternative to stromal puncture.

- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.

- Persistent epithelial defects and ulcerations that do not respond to conservative therapy.

- Severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.
• Moderate or severe acute ocular chemical burn.

• Corneal perforation when corneal tissue is not immediately available.

• Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Practice Guidelines and Position Statements

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.39 The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, “healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.” References from two randomized controlled trials on dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

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.23 The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

• Step 1:
  o Education regarding the condition, its management, treatment and prognosis
  o Modification of local environment
  o Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
  o Identification and potential modification/elimination of offending systemic and topical medications
  o 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):
  o Non-preserved ocular lubricants to minimize preservative-induced toxicity
  o Tea tree oil treatment for Demodex (if present)
  o Tear conservation
  o Punctal occlusion
  o Moisture chamber spectacles/goggles
  o Overnight treatments (such as ointment or moisture chamber devices)
  o In-office, physical heating and expression of the meibomian glands
  o In-office intense pulsed light therapy for meibomian gland dysfunction
  o Prescription drugs to manage dry eye disease
    o Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  o Topical corticosteroid (limited-duration)
  o Topical secretagogues
  o Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
  o Topical LFA-1 antagonist drugs (such as lifitegrast)
  o Oral macrolide or tetracycline antibiotics

• Step 3 (if above options are inadequate consider):
  o Oral secretagogues
  o Autologous/allogeneic serum eye drops
  o Therapeutic contact lens options
  o Soft bandage lenses
  o Rigid scleral lenses
• Step 4 (if above options are inadequate consider):
  o Topical corticosteroid for longer duration
  o Amniotic membrane grafts
  o Surgical punctal occlusion
  o Other surgical approaches (eg tarsorrhaphy, 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, 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.”

Medicare National Coverage

There is no national coverage determination.

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).

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:

- "The HCT/P is minimally manipulated;
- The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;
- 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
- Either:
  - 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
  - The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
    - Is for autologous use;
    - Is for allogeneic use in a first-degree or second-degree blood relative; or
    - Is for reproductive use."

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

- "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.
- 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.
- 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 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.

References


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### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/01/20</td>
<td>New policy, approved July 14, 2020. Policy replaces 7.01.149. AmnioFix added as investigational. All other policy statements remain unchanged.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>10/01/20</td>
<td>Coding update. Added HCPCS codes Q4249, Q4250, Q4254, Q4255.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2021 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action before a date, to keep your health insurance or assistance. You have the right to free information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Chinese (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內容可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或協助金額。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Arabic (Arabic):
يسري هذا الإشعار عنษRONinformation to مراجعات ينفع في إعداد الحالة العربية التي تريد الحصول عليها من خلال حمل هذا الإشعار. قد تحتاج إلى إعداد حالة في الوثيقة. يتم تعديل هذه المعلومات على تطبيق تلك الصورة أو المستخدمة في الدم الكاذب. يلزم ذلك الحصول على هذه المعلومات والمساعدة بذلك دون تكلفة أصلية. اتصل 800-722-1471 (TTY: 800-842-5357)

Italiano (Italian):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

ไทย (Thai):
ประกาศนี้มีสาระสำคัญ ประกาศนี้มีสาระสำคัญเกี่ยวกับการขอรับการช่วยเหลือในการประกันสุขภาพของคุณ Premera Blue Cross และการมีส่วนร่วมในการประกันสุขภาพของคุณ การมีส่วนร่วมในประกาศนี้ คุณจะมีสิทธิที่จะรับข้อมูลและการช่วยเหลือในการประกันสุขภาพของคุณได้ โปรดติดต่อ โทร 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

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この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または保険範囲に関する重要な情報が含まれている場合があります。この通知には記載されている情報が有効な重要な日付をご確認ください。健康保険や料金サポートを維持するには、特定の期限を越えて行動を取るわけならなりません。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지에 관한 정보를 포함하고 있는 경우 있습니다. 본 통지서에는 백신이 되는 복강파일들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어에 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시오.

세로운 방식으로, 다양한 언어로 작성된 정보가 제공됩니다. 이는 고객이 자신의 언어로 정보를 이해하고, 필요에 따라 지원을 받을 수 있도록 하는데 도움이 됩니다. 예를 들어, 영어, 프랑스어, 스페인어, 독일어, 일본어, 중국어, 그리고 한국어 등 다양한 언어로 정보가 제공됩니다. 각 언어별로 정보는 문맥에 따라 다르며, 주요한 정보는 뚜렷하게 표시되며, 사용자에게 정보를 얻기 위한 단계에 대한 지침도 제공됩니다.

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