PREMERA HMO

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# MEDICAL POLICY – 7.01.583

# Amniotic Membrane and Amniotic Fluid

| | |
|---|---|
| BCBSA Ref. Policy: | 7.01.149 |
| Effective Date: | Jul. 1, 2025 |
| Last Revised: | Jul. 3, 2025 |
| Replaces: | N/A |

RELATED MEDICAL POLICIES:

| | |
|---|---|
| 2.01.543 | Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions |
| 7.01.582 | Bioengineered Skin and Soft Tissue Substitutes |
| 8.01.52 | Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow) |

**Select a hyperlink below to be directed to that section.**

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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## 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 injections of 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

| Service | Medical Necessity |
|---|---|
| **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:**<br>• Affinity<br>• AmnioBand Membrane<br>• Biovance<br>• EpiCord<br>• Epifix<br>• Grafix<br>• NuShield<br><br>***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 (e.g., Zelen et al, 2015).<br><br>**When the above medical necessity criteria are met, the following conditions of coverage will apply:**<br>• Treatment is limited to a maximum of 6 applications in 12 weeks when evidence of wound healing is present<br><br>**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).**<br><br>**Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.** |
| **Human amniotic membrane grafts for ophthalmic indications** | **Human amniotic membrane grafts with or without suture or glue may be considered medically necessary for the treatment of ophthalmic conditions** |

| Service | Investigational |
|---|---|
| **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:**<br>• Osteoarthritis<br>• Plantar fasciitis |
| **Injection of human amniotic fluid** | **Injection of human amniotic fluid is considered investigational for all indications.** |
| **All other human amniotic products** | **All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered investigational** |
| **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 and repair following Mohs micrographic surgery.** |
| **All other human amnionic membrane products** | **All other human amniotic membrane products not listed above are considered investigational, including but not limited to, those listed in the Coding section of this policy in the Investigational (Not Eligible for Coverage) subsection.** |

**Note:**

| Documentation Requirements |
|---|
| **The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:**<br>• Diagnosis/condition<br>• History and physical examination documenting the severity of the condition<br>• Name of product to be used<br>• Previous therapy attempted and for how long<br>• The size (measurements) of the affected area to be treated |

## Coding

Note: This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products.

| Code | Description |
|---|---|
| **HCPCS** | |
| **Reviewed for Medical Necessity** | |
| | |
| Q4132 | Grafix Core and GrafixPL Core, per sq cm |
| Q4133 | Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter |
| Q4151 | AmnioBand or Guardian, per sq cm |
| Q4154 | Biovance, per sq cm |
| Q4159 | Affinity, per sq cm |
| Q4160 | Nushield, per sq cm |
| Q4186 | Epifix, per square centimeter |
| Q4187 | EpiCord, per square centimeter |
| **Investigational (Not Eligible for Coverage)** | |
| A2035 | Corplex p or theracor p or allacor p, per milligram (new code effective 04/01/25) |
| Q4100 | Skin substitute, not otherwise specified (e.g., AmnioFix) |
| Q4137 | AmnioExcel, AmnioExcel Plus or Biodexcel, per sq cm |
| Q4138 | BioDFence DryFlex, per sq cm |
| Q4139 | AmnioMatrix or BioDMatrix, injectable, 1 cc. |
| Q4140 | BioDFence, per sq cm |
| Q4145 | EpiFix, injectable, 1 mg |
| Q4148 | Neox Cord 1k, Neox Cord-RT, or Clarix Cord 1K, per sq cm |
| Q4150 | AlloWrap DS or dry, per square centimeter |
| Q4153 | Dermavest and Plurivest, per sq cm |
| Q4155 | NeoxFlo or Clarix Flo, 1 mg |
| Q4156 | Neox 100 or Clarix 100, per sq cm (e.g., NeoxWound) |
| Q4157 | Revitalon, per sq cm |
| | |
| Q4162 | WoundEx Flow, BioSkin Flow, 0.5 cc (e.g., BioSkin) |

| Code | Description |
|---|---|
| Q4163 | WoundEx,, BioSkin,, per sq cm |
| Q4168 | AmnioBand, 1 mg (Particulate) |
| Q4169 | Artacent Wound, per sq cm |
| Q4170 | Cygnus per sq cm |
| Q4171 | Interfyl, 1 mg |
| Q4173 | PalinGen or PalinGen XPlus, per sq cm (e.g., PalinGen Membrane) |
| Q4174 | PalinGen or ProMatrX, 0.36 mg per 0.25 cc (e.g., PalinGen SportFlow, ProMatrX liquid) |
| Q4176 | Neopatch or Therion, per square centimeter |
| Q4177 | FlowerAmnioFlo, 0.1 cc |
| Q4178 | FlowerAmnioPatch, per sq cm |
| Q4180 | Revita, per sq cm |
| Q4181 | Amnio Wound, per sq cm |
| Q4183 | SurgiGRAFT, per square centimeter |
| Q4184 | Cellesta or Cellesta Duo, per square centimeter |
| Q4185 | Cellesta flowable amnion (25 mg per cc); per 0.5 cc |
| Q4188 | AmnioArmor, per square centimeter |
| Q4189 | Artacent AC, 1 mg (flowable) |
| Q4190 | Artacent AC, per square centimeter (patch) |
| Q4191 | Restorigin, per square centimeter |
| Q4192 | Restorigin, 1 cc (injectable) |
| Q4194 | Novachor, per square centimeter |
| Q4198 | Genesis Amniotic Membrane, per square centimeter |
| Q4199 | Cygnus Matrix, per sq cm |
| Q4201 | Matrion, per sq cm |
| Q4202 | Keroxx (2.5 g/cc), 1 cc |
| Q4204 | XWRAP, per square centimeter |

| Code | Description |
|---|---|
| Q4205 | Membrane Graft or Membrane Wrap, per sq cm |
| Q4206 | Fluid Flow or Fluid GF, 1 cc |
| Q4208 | Novafix, per sq cm |
| Q4209 | SurGraft, per sq cm |
| Q4210 | Axolotl Graft or Axolotl DualGraft, per sq cm (code termed effective 07/01/24) |
| Q4211 | Amnion Bio or AxoBioMembrane, per sq cm |
| Q4212 | AlloGen, per cc |
| Q4213 | Ascent, 0.5 mg |
| Q4214 | Cellesta Cord, per sq cm |
| Q4215 | Axolotl Ambient or Axolotl Cryo, 0.1 mg |
| Q4216 | Artacent Cord, per sq cm |
| Q4217 | WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm |
| Q4218 | SurgiCORD, per sq cm |
| Q4219 | SurgiGRAFT-DUAL, per sq cm |
| Q4221 | Amnio Wrap2, per sq cm |
| Q4224 | Human Health Factor 10 amniotic patch (hhf10-p), per square centimeter |
| Q4225 | AmnioBind, per square centimeter |
| Q4227 | AmnioCore per sq cm |
| Q4229 | Cogenex Amniotic Membrane, per sq cm |
| Q4230 | Cogenex Flowable Amnion, per 0.5 cc |
| Q4231 | Corplex P, per cc |
| Q4232 | Corplex, per sq cm |
| Q4233 | SurFactor or NuDyn, per 0.5 cc |
| Q4234 | XCellerate, per sq cm |
| Q4235 | Amniorepair or AltiPly, per sq cm |
| Q4236 | CarePATCH, per sq cm |

| Code | Description |
|---|---|
| Q4237 | Cryo-Cord, per sq cm |
| Q4239 | Amnio-maxx or Amnio-maxx Lite, per sq cm |
| Q4240 | CoreCyte, for topical use only, per 0.5 cc |
| Q4241 | PolyCyte, for topical use only, per 0.5 cc |
| Q4242 | AmnioCyte Plus, per 0.5 cc (e.g., AmnioCyte) |
| Q4245 | Amniotext, per cc |
| Q4246 | CoreText or ProText, per cc |
| Q4247 | Amniotext patch, per sq cm |
| Q4248 | Dermacyte Amniotic Membrane Allograft, per sq cm |
| Q4249 | Amniply, for topical use only, per square centimeter |
| Q4250 | AmnioAmp-MPMP, per square centimeter |
| Q4251 | Vim, per sq cm |
| Q4252 | Vendaje, per sq cm |
| Q4253 | Zenith Amniotic Membrane, per sq cm |
| Q4254 | Novafix DL, per square centimeter |
| Q4255 | REGUaRD, for topical use only, per square centimeter |
| Q4256 | MLG-CompleteTM, per square centimeter |
| Q4257 | Release, per square centimeter |
| Q4258 | Enverse, per square centimeter |
| Q4259 | celera Dual Layer or celera Dual Membrane, per sq cm |
| Q4260 | Signature APatch, per sq cm |
| Q4261 | TAG, per sq cm |
| Q4262 | Dual Layer Impax Membrane, per sq cm |
| Q4263 | SurGraft TL, per sq cm |
| Q4264 | Cocoon Membrane, per sq cm |
| Q4265 | Neostim TL, per square centimeter |

| Code | Description |
|---|---|
| Q4266 | Neostim membrane, per square centimeter |
| Q4267 | Neostim DL, per square centimeter |
| Q4268 | SurGraft FT, per square centimeter |
| Q4269 | SurGraft XT, per square centimeter |
| Q4270 | Complete SL, per square centimeter |
| Q4271 | Complete FT, per square centimeter |
| Q4272 | Esano a, per square centimeter |
| Q4273 | Esano aaa, per square centimeter |
| Q4274 | Esano ac, per square centimeter |
| Q4275 | Esano aca, per square centimeter |
| Q4276 | Orion, per square centimeter |
| Q4277 | Woundplus membrane or e-graft, per square centimeter (code terminated effective 07/01/24) |
| Q4278 | Epieffect, per square centimeter |
| Q4279 | Vendaje AC, per sq cm |
| Q4280 | Xcell amnio matrix, per square centimeter |
| Q4281 | Barrera sl or barrera dl, per square centimeter |
| Q4282 | Cygnus dual, per square centimeter |
| Q4283 | Biovance tri-layer or biovance 3l, per square centimeter |
| Q4284 | Dermabind sl, per square centimeter |
| Q4285 | Nudyn dl or nudyn dl mesh, per square centimeter |
| Q4286 | Nudyn sl or nudyn slw, per square centimeter |
| Q4287 | DermaBind DL, per sq cm |
| Q4288 | DermaBind CH, per sq cm |
| Q4289 | RevoShield+ Amniotic Barrier, per sq cm |
| Q4290 | Membrane Wrap-Hydro™, per sq cm |
| Q4291 | Lamellas XT, per sq cm |

| Code | Description |
|---|---|
| Q4292 | Lamellas, per sq cm |
| Q4293 | Acesso DL, per sq cm |
| Q4294 | Amnio Quad-Core, per sq cm |
| Q4295 | Amnio Tri-Core Amniotic, per sq cm |
| Q4296 | Rebound Matrix, per sq cm |
| Q4297 | Emerge Matrix, per sq cm |
| Q4298 | AmniCore Pro, per sq cm |
| Q4299 | AmniCore Pro+, per sq cm |
| Q4300 | Acesso TL, per sq cm |
| Q4301 | Activate Matrix, per sq cm |
| Q4302 | Complete ACA, per sq cm |
| Q4303 | Complete AA, per sq cm |
| Q4304 | GRAFIX PLUS, per sq cm |
| Q4305 | American amnion ac tri-layer, per square centimeter |
| Q4306 | American amnion ac, per square centimeter |
| Q4307 | American amnion, per square centimeter |
| Q4308 | Sanopellis, per square centimeter |
| Q4309 | Via matrix, per square centimeter |
| Q4310 | Procenta, per 100 mg |
| Q4311 | Acesso, per square centimeter |
| Q4312 | Acesso ac, per square centimeter |
| Q4313 | Dermabind fm, per square centimeter |
| Q4314 | Reeva ft, per square cenitmeter |
| Q4315 | Regenelink amniotic membrane allograft, per square centimeter |
| Q4316 | Amchoplast, per square centimeter |
| Q4317 | Vitograft, per square centimeter |

| Code | Description |
|---|---|
| Q4318 | E-graft, per square centimeter |
| Q4319 | Sanograft, per square centimeter |
| Q4320 | Pellograft, per square centimeter |
| Q4321 | Renograft, per square centimeter |
| Q4322 | Caregraft, per square centimeter |
| Q4323 | Alloply, per square centimeter |
| Q4324 | Amniotx, per square centimeter |
| Q4325 | Acapatch, per square centimeter ( |
| Q4326 | Woundplus, per square centimeter |
| Q4327 | Duoamnion, per square centimeter |
| Q4328 | Most, per square centimeter |
| Q4329 | Singlay, per square centimeter |
| Q4330 | Total, per square centimeter |
| Q4331 | Axolotl graft, per square centimeter |
| Q4332 | Axolotl dualgraft, per square centimeter |
| Q4333 | Ardeograft, per square centimeter |
| Q4334 | Amnioplast 1, per square centimeter (new code effective 10/01/24) |
| Q4335 | Amnioplast 2, per square centimeter (new code effective 10/01/24) |
| Q4336 | Artacent c, per square centimeter (new code effective 10/01/24) |
| Q4337 | Artacent trident, per square centimeter (new code effective 10/01/24) |
| Q4338 | Artacent velos, per square centimeter (new code effective 10/01/24) |
| Q4339 | Artacent vericlen, per square centimeter (new code effective 10/01/24) |
| Q4340 | Simpligraft, per square centimeter (new code effective 10/01/24) |
| Q4341 | Simplimax, per square centimeter (new code effective 10/01/24) |
| Q4342 | Theramend, per square centimeter (new code effective 10/01/24) |
| Q4343 | Dermacyte ac matrix amniotic membrane allograft, per square centimeter (new code effective 10/01/24) |

| Code | Description |
|---|---|
| Q4344 | Tri-membrane wrap, per square centimeter (new code effective 10/01/24) |
| Q4345 | Matrix hd allograft dermis, per square centimeter (new code effective 10/01/24) |
| Q4346 | Shelter dm matrix, per square centimeter (new code effective 01/01/2025) |
| Q4347 | Rampart dl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4348 | Sentry sl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4349 | Mantle dl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4350 | Palisade dm matrix, per square centimeter (new code effective 01/01/2025) |
| Q4351 | Enclose tl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4352 | Overlay sl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4353 | Xceed tl matrix, per square centimeter (new code effective 01/01/2025) |
| Q4354 | Palingen dual-layer membrane, per square centimeter (new code effective 04/01/25) |
| Q4355 | Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter (new code effective 04/01/25) |
| Q4356 | Abiomend membrane and abiomend hydromembrane, per square centimeter (new code effective 04/01/25) |
| Q4357 | Xwrap plus, per square centimeter (new code effective 04/01/25) |
| Q4358 | Xwrap dual, per square centimeter (new code effective 04/01/25) |
| Q4359 | Choriply, per square centimeter (new code effective 04/01/25) |
| Q4360 | Amchoplast fd, per square centimeter (new code effective 04/01/25) |
| Q4361 | Epixpress, per square centimeter (new code effective 04/01/25) |
| Q4362 | Cygnus disk, per square centimeter (new code effective 04/01/25) |
| Q4363 | Amnio burgeon membrane and hydromembrane, per square centimeter (new code effective 04/01/25) |
| Q4364 | Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter (new code effective 04/01/25) |
| Q4365 | Amnio burgeon dual-layer membrane, per square centimeter (new code effective 04/01/25) |
| Q4366 | Dual layer amnio burgeon x-membrane, per square centimeter (new code effective 04/01/25) |

| Code | Description |
|---|---|
| Q4367 | Amniocore sl, per square centimeter (new code effective 04/01/25) |
| Q4368 | AmchoThick, per sq cm (new code effective 07/01/25) |
| Q4369 | AmnioPlast 3, per sq cm (new code effective 07/01/25) |
| Q4370 | AeroGuard, per sq cm (new code effective 07/01/25) |
| Q4371 | NeoGuard, per sq cm (new code effective 07/01/25) |
| Q4372 | AmchoPlast EXCEL, per sq cm (new code effective 07/01/25) |
| Q4373 | Membrane Wrap-Lite, per sq cm (new code effective 07/01/25) |
| Q4375 | duoGRAFT AC, per sq cm (new code effective 07/01/25) |
| Q4376 | Duograft AA, per sq cm (new code effective 07/01/25) |
| Q4377 | triGRAFT FT, per sq cm (new code effective 07/01/25) |
| Q4378 | Renew FT Matrix, per sq cm (new code effective 07/01/25) |
| Q4379 | AmnioDefend FT Matrix, per sq cm (new code effective 07/01/25) |
| Q4380 | AdvoGraft One, per sq cm (new code effective 07/01/25) |
| Q4382 | AdvoGraft Dual, per sq cm (new code effective 07/01/25) |

**Note**: HRT: Human Regenerative Technologies; MTF Musculoskeletal Transplant Foundation. [a] Processed by HRT and marketed under different tradename.



## Related Information

### 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 $cm^2$)

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

## Table 1. Epifix Sample of Package Standard Sizes

| Item Number | Size & Description |
|---|---|
| GS-5140 | 14 mm disk (1.5 sq cm) |
| GS-5160 | 16 mm disk (2 sq cm) |
| GS-5180 | 18 mm disk (2.5 sq cm) |
| GS-5024 | 24 mm disk (4.5 sq cm) |
| GS-5220 | 2 cm x 2 cm sheet (4 sq cm) |
| GS-5230 | 2 cm x 3 cm sheet (6 sq cm) |
| Gs-5240 | 2 cm x 4 cm sheet (8 sq cm) |
| GS-5330 | 3 cm x 3 cm sheet (9 sq cm) |
| GS-5340 | 3 cm x 4 cm sheet (12 sq cm) |
| GS-5440 | 4 cm x 4 cm sheet (16 sq cm) |
| GS-5350 | 3 cm x 5 cm sheet (15 sq cm) |
| GS-5460 | 4 cm x 6 cm sheet (24 sq cm) |
| GS-5560 | 5 cm x 6 cm sheet (30 sq cm) |
| GS-5770 | 7 cm x 7 cm sheet (49 sq cm) |
| ES-2300 | 2 cm x 3 cm mesh sheet (4 sq cm) |
| ES-3300 | 3.5 x 3.5 cm mesh sheet (8 sq. cm) |
| ES-3500 | 3 cm x 5 cm mesh sheet (10 sq cm) |
| ES-4400 | 4 cm x 4.5 cm mesh sheet (10.2 sq cm) |
| ES-5500 | 5 cm x 5.5 cm mesh sheet (16.1 sq cm) |

Source: **https://mimedx.com/epifix/** (Accessed June 2, 2025).

## Table 2. AmnioBand Sizing Guidelines

| Tissue Code | Product Specifications |
|---|---|
| WC3010 | AmnioBand Membrane, 10mm Disk |
| WC3014 | AmnioBand Membrane, 14mm Disk |
| WC3016 | AmnioBand Membrane, 16mm Disk |

| Tissue Code | Product Specifications |
|---|---|
| WC3018 | AmnioBand Membrane, 18mm Disk |
| WC3022 | AmnioBand Membrane, 2cm x 2cm |
| WC3023 | AmnioBand Membrane, 2cm x 3cm |
| WC3024 | AmnioBand Membrane, 2cm x 4cm |
| WC3034 | AmnioBand Membrane, 3cm x 4cm |
| WC3044 | AmnioBand Membrane, 4cm x 4cm |
| WC3038 | AmnioBand Membrane, 3cm x 8cm |
| WC3046 | AmnioBand Membrane, 4cm x 6cm |
| WC3056 | AmnioBand Membrane, 5cm x 6cm |
| WC3077 | AmnioBand Membrane, 7cm x 7cm |

Source: **https://www.mtfbiologics.org/our-products/detail/amnioband-membrane** (June 2, 2025).

## Table 3. Other Product Size Specifications

| Name | Available Sizes | Link |
|---|---|---|
| Affinity | 1.5 x 1.5 cm (2.25 square cm)<br>2.5 x 2.5 cm (6.25 square cm) | **https://affinityfresh.com/why-choose-affinity/product-details-and-resources.html** |
| Biovance | 1 cm x 2 cm<br>2 cm x 2 cm<br>2 cm x 3 cm<br>2 cm x 4 cm<br>3 cm x 3.5 cm<br>4 cm x 4 cm<br>5 cm x 5 cm<br>6 cm x 6 cm | **https://cdn.arthrex.io/image/upload/dec74ab9-9ca5-4c07-9052-fe1bbf6e4a2c.pdf** |
| Epicord | 1 cm x 2 cm (2 sq cm)<br>2 cm x 3 cm (6 sq cm)<br>3 cm x 5 cm (15 sq cm)<br>2 cm x 3 cm (6 sq cm)<br>Epicord Expandable | **https://mimedx.com/epicord/**<br>(see product details, other information) |
| Grafix | 16 mm Disc (2 $cm^2$)<br>1.5 cm x 2 cm (3 $cm^2$)<br>2 cm x 3 cm (6 $cm^2$) | **https://www.grafixpl.com/products** |

| Name | Available Sizes | Link |
|---|---|---|
| | 3 cm x 3 cm (9 cm²)<br>3 cm x 4 cm (12 cm²)<br>5 cm x 5 cm (25 cm²)<br>7 cm x 7 cm (49 cm²)<br>7.5 cm x 15 cm (113 cm²) | |
| Nushield | 1.4 cm disc (2 billable units) | **https://www.nushieldcomplete.com/product-details-resources/** |

## 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

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

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.[1] There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered non-immunogenic and has not been observed to cause a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and HAM products, resulting in a readily available tissue with regenerative potential. In support, one 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 pre-clinical 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 formulation of HAM or placental membrane (i.e., Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix, NuShield), 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 (i.e., Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix, NuShield), 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 an 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 formulation of HAM, the evidence includes 3 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 and 1 multicenter RCT with Amnioband. 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. The third RCT demonstrated significantly greater blinded assessor-confirmed rates of complete wound closure at 12 weeks after weekly or twice-weekly application of AmnioBand Membrane with compression bandaging compared with compression bandaging alone. The evidence is sufficient 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

For individuals who have plantar fasciitis who receive an injection of amniotic membrane, the evidence 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 an improvement 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. Based on clinical input received in 2019, it was determined that there is a clinically meaningful improvement in the net health outcome and the use of HAM is consistent with generally accepted medical practice for the treatment of ophthalmic conditions.

## Repair Following Mohs Micrographic Surgery

For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from

medical records compared a dehydrated human amnionic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of individuals requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of individuals who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (p<.0001). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 4**.

## Table 4. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| **Ongoing** | | | |
| NCT06600724[a] | A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Evaluating PURION Processed Lyophilized Human Amnion/Chorion Membrane (ppLHACM) and Standard of Care Versus Standard of Care Alone in the Treatment of Nonhealing Diabetic Foot Ulcers | 170 | Aug 2026 |
| NCT04457752[a] | 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 | 124 | Mar 2023 |
| NCT03390920[a] | Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions | 200 | Jan 2030 |
| NCT04553432[a] | Dry Eye OmniLenz Application of Omnigen Research Study | 79 (actual) | Jul 2023 |
| NCT04636229[a] | 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 | 474 | Jun 2025 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT06000410[a] | 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 | 474 | Mar 2026 |
| NCT05842057[a] | Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER) | 240 | Aug 2028 |
| NCT06150209[a] | A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients | 100 | Jun 2025 |
| NCT05796765[a] | A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee | 43 (terminated) | Dec 2023 |
| **Unpublished** | | | |
| NCT03855514[a] | A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers | 200 | Dec 2021 |
| NCT04599673 | Prospective Analysis of Intraoperative AMNIOGEN Injection in Patients With Rotator Cuff Tear | 100 | Sep 2022 |
| NCT04612023 | A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee | 90 | Jul 2022 |

NCT: national clinical trial.

[a] 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.

## Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## 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."[46]

## Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[47] 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 amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

## Medicare National Coverage

There is no national coverage determination.

## Regulatory Status

In 2024, the US Food and Drug Administration (FDA) issued a public safety notification on amniotic fluid eyedrops.[4] The notice was to inform the public and health care practitioners "that manufacturers are marketing and distributing amniotic fluid eyedrops to treat, mitigate, or cure diseases or conditions such as dry eye disease without the required premarket review and approval, raising potential significant safety concerns." A list of related warning letters issued by the FDA can be found on the FDA website's Warning Letters page using the search term "amniotic fluid."[5]

On December 19, 2024, the FDA issued a warning letter to Integra LifeSciences Corporation stating: "FDA investigators and a microbiologist determined that the above firms manufacture a variety of neurological and neurosurgical devices, including but not limited to, cranial perforators, disposable cottonoid patties and strips as well as collagen based medical devices, that are used for wound care, soft tissue repair and reconstruction surgery. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body."[6]

The 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).[7]

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);

product code NQB. 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."[8] The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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## History

| Date | Comments |
|---|---|
| 08/01/20 | New policy, approved July 14, 2020. Policy replaces 7.01.149. AmnioFix added as investigational. All other policy statements remain unchanged. |
| 10/01/20 | Coding update. Added HCPCS codes Q4249, Q4250, Q4254, Q4255. |
| 05/01/21 | Annual Review, approved April 13, 2021. Policy updated with literature review through December 28, 2020; references added. Affinity added to medically necessary statement for the treatment of diabetic foot ulcers; edits made to investigational statement on human amniotic products. |
| 10/01/21 | Coding update, Added HCPCS codes Q4251, Q4252 and Q4253. |
| 1/1/2022 | Coding update, Added HCPCS codes A2001 and Q4199. |
| 05/01/22 | Annual Review, approved April 12, 2022. Policy updated with literature review through January 3, 2022; references added. Added investigational statement for treatment following Mohs microsurgery and all other human amniotic products not listed. Modified medically necessary statement for ophthalmic conditions to a general statement rather than listing specific indications. Removed code A2001 InnovaMatrix AC (new code effective 1/1/22) as it was moved to policy 7.01.113 since it is a skin substitute. Added new CPT codes Q4224, Q4225, Q4256, Q4257, and Q4258. Added new product names AmnioBind, Relese, MLG-CompleteTM, and Enverse. |
| 07/01/22 | Coding update. Added HCPC codes Q4259, Q4260 and Q4261. |
| 12/01/22 | Coding update. Added AmnioFix as it was inadvertently deleted in error. |
| 01/01/23 | Coding update. Added new HCPC codes Q4236, Q4262, Q4263, & Q4264. |
| 04/01/23 | Coding update. Removed Derm-maxx name from product table. Added new HCPC codes Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271. Added product names NeoStim DL, NeoStim TL, NeoStim membrane, SurGraft FT, SurGraft XT, Complete FT, and Complete SL. |

| Date | Comments |
|---|---|
| 05/01/23 | Annual Review, approved April 10, 2023. Policy updated with literature review through January 20, 2023; no references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization. Removed Surgenex from product table. |
| 07/01/23 | Coding update. Added new HCPCS codes Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283, Q4284. |
| 10/01/23 | Coding update. Added new HCPCS codes Q4285 and Q4286. |
| 01/01/24 | Coding update. Added new HCPCS codes Q4279 and Q4287-Q4304. |
| 04/01/24 | Coding Update. Added new HCPCS codes Q4305-Q4310 and termed HCPCS code Q4244. |
| 05/22/24 | Coding Update. Added new HCPCS codes Q4311, Q4312, Q4313, Q4314, Q4315, Q4316, Q4317, Q4318, Q4319, Q4320, Q4321, Q4322, Q4323, Q4324, Q4325, Q4326, Q4327, Q4328, Q4329, Q4330, Q4331, Q4332, Q4333, |
| 06/01/24 | Annual Review, approved May 23, 2024. Policy updated with literature review through January 3, 2024; reference added. Policy statements unchanged. HCPCS code Q4228 termed 10/01/2021. |
| 07/01/24 | Coding update. Termed HCPCS codes Q4210 and Q4277. |
| 10/01/24 | Coding update. Added new HCPCS codes Q4334, Q4335, Q4336, Q4337, Q4338, Q4339, Q4340, Q4341, Q4342, Q4343, Q4344, Q4345. |
| 01/01/25 | Coding update. Added new HCPCS codes Q4346, Q4347, Q4348, Q4349, Q4350, Q4351, Q4352, Q4353. Minor update to related policy. 2.01.16 was replaced with 2.01.543 Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions. |
| 04/01/25 | Coding update. Added new HCPCS codes A2035, Q4354, Q4355, Q4356, Q4357, Q4358, Q4359, Q4360, Q4361, Q4362, Q4363, Q4364, Q4365, Q4366, Q4367. |
| 07/01/25 | Annual Review, approved June 10, 2025. Policy updated with literature review through February 21, 2025; references added. NuShield added to existing medically necessary policy statement for the treatment of nonhealing diabetic lower-extremity ulcers. Otherwise, policy statements unchanged. Added new HCPCS codes: Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4378, Q4379, Q4380, Q4382 due to Q3 coding updates. |
| 07/03/25 | Minor update made to Related Policy section. Policy 7.01.113 Bioengineered Skin and Soft Tissue Substitutes is deleted and replaced with 7.01.582 Bioengineered Skin and Soft Tissue Substitutes. |



**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.