

**EFFECTIVE DATE:** 09|01|2018

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## OVERVIEW

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.

## MEDICAL CRITERIA

Not applicable

## PRIOR AUTHORIZATION

Not applicable

## POLICY STATEMENT

### BlueCHiP for Medicare and Commercial Products

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

Sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis
- Corneal ulcers and melts
- Pterygium repair
- Stevens-Johnson syndrome
- Persistent epithelial defects

### BlueCHiP for Medicare

Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

Injection of micronized or particulated human amniotic membrane and injection of human amniotic fluid is not covered for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

### Commercial Products

Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

Injection of micronized or particulated human amniotic membrane and injection of human amniotic fluid is considered not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable surgery and not medically necessary/not covered benefits/coverage.

## **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 1).

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

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

### **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.<sup>1</sup> 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.<sup>3</sup> 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.

#### **Diabetic Lower-Extremity Ulcers**

For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (ie, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. Results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product.

#### **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 is insufficient to determine the effects of the technology on health outcomes. Well-designed and well-conducted random controlled trials that compare HAM with the standard of care for venous insufficiency ulcers are needed.

#### **Osteoarthritis**

For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence is insufficient to determine the effects of the technology on health outcomes.

### **Plantar Fasciitis**

For individuals who have plantar fasciitis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence is insufficient to determine the effects of the technology on health outcomes.

### **Ophthalmic Conditions**

For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic conditions who receive HAM without suture, the evidence is insufficient to determine the effects of the technology on health outcomes.

## **CODING**

### **BlueCHiP for Medicare and Commercial Products**

The following HCPCS codes are considered medically necessary when filed with the ICD-10 diagnosis codes listed below.

- Q4131 EpiFix or Epicord, per square centimeter
- Q4132 Grafix core and GrafixPL core, per square centimeter
- Q4133 Grafix prime and GrafixPL prime, per square centimeter
- Q4137 Amnioexcel or BioDExCel, per square centimeter
- Q4138 Biodfence Dryflex, per square centimeter
- Q4139 AmnioMatrix or BioDMatrix, injectable, 1 cc
- Q4140 Biodfence, per square centimeter
- Q4145 Epifix, injectable, 1 mg
- Q4148 Neox cord 1k, Neox cord RT, or Clarix cord 1K, per square centimeter
- Q4150 AlloWrap DS or dry, per square centimeter
- Q4151 AmnioBand or Guardian, per square centimeter
- Q4153 Dermavest and Plurivest, per square centimeter
- Q4154 Biovance, per square centimeter
- Q4155 Neoxflo or Clarixflo, 1 mg
- Q4156 Neox 100 or Clarix 100, per square centimeter
- Q4157 Revitalon, per square centimeter
- Q4159 Affinity, per square centimeter
- Q4160 NuShield, per square centimeter
- Q4162 WoundEx Flow, BioSkin Flow, 0.5 cc
- Q4163 WoundEx, BioSkin, per square centimeter
- Q4168 Amnioband, 1 mg
- Q4169 Artacent wound, per square centimeter
- Q4170 Cygnus, per square centimeter
- Q4171 Interfyl, 1 mg
- Q4173 PalinGen or PalinGen XPlus, per square centimeter
- Q4174 PalinGen or ProMatrX, 0.36 mg per 0.25 cc

If no specific HCPCS code exists for a product (e.g. AmnioFix or OrthoFlo), an appropriate unlisted code, such as Q4100, would be used.

## ICD-10 Diagnosis Codes that may support medical necessity:

E08.621-E08.622	H11.001-H11.069
E09.621-E09.622	H16.001-H16.079
E10.621-E10.622	H16.231-H16.239
E11.621-E11.622	H18.831-H18.839
E13.621-E13.622	L51.1

## RELATED POLICIES

Not applicable

## PUBLISHED

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## REFERENCES

1. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine? *Regen Med.* Mar 2009;4(2):275-291. PMID 19317646
2. Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. *Int Wound J.* Oct 2013;10(5):493-500. PMID 23902526
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. *J Bone Joint Surg.* 1938;20(1):167-177. PMID
4. Food and Drug Administration. 510(k) Summary: ProKera™ Bio-Tissue Inc. (K032104). 2003; [https://www.accessdata.fda.gov/cdrh\\_docs/pdf3/K032104.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf). Accessed January 26, 2018.
5. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open.* Oct 2016;4(10):e1095. PMID 27826487
6. Snyder RJ, Shimozaki K, Tallis A, et al. A prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of care for the closure of chronic diabetic foot ulcer. *Wounds.* Mar 2016;28(3):70-77. PMID 26978860
7. Smiell JM, Treadwell T, Hahn HD, et al. Real-world experience with a decellularized dehydrated human amniotic membrane allograft. *Wounds.* Jun 2015;27(6):158-169. PMID 26061491
8. Zelen CM, Serena TE, Denoziere G, et al. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J.* Oct 2013;10(5):502-507. PMID23742102
9. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long term follow-up study. *Wound Med.* 2014;4:1-4. PMID
10. Zelen CM, Serena TE, Snyder RJ. A prospective, randomised comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. *Int Wound J.* Apr 2014;11(2):122-128. PMID 24618401
11. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J.* Dec 2015;12(6):724-732. PMID 25424146
12. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int Wound J.* Apr 2016;13(2):272-282. PMID 26695998
13. Kirsner RS, Sabolinski ML, Parsons NB, et al. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen.* Sep 2015;23(5):737-744. PMID 26100572

14. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J*. Oct 2014;11(5):554-560. PMID 25048468
15. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. *Wound Repair and Regeneration*. Nov-Dec 2014;22(6):688-693. PMID 25224019
16. Serena TE, Yaakov R, DiMarco D, et al. Dehydrated human amnion/chorion membrane treatment of venous leg ulcers: correlation between 4-week and 24-week outcomes. *J Wound Care*. Nov 2015;24(11):530-534. PMID 26551645
17. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix(R)) allograft for the treatment of venous leg ulcers. *Int Wound J*. Oct 11 2017. PMID 29024419
18. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved amniotic suspension for the treatment of knee osteoarthritis. *J Knee Surg*. Aug 2016;29(6):443-450. PMID 26683979
19. Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. *Br J Sports Med*. Nov 2016;50(22):1367-1375. PMID 27143138
20. Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. *Foot Ankle Int*. Feb 2015;36(2):151-158. PMID 25249320
21. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. *Foot Ankle Int*. Oct 2013;34(10):1332-1339. PMID 23945520
22. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea*. Aug 2005;24(6):654-660. PMID 16015082
23. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. *Ophthalmology*. Jan 2013;120(1):201-208. PMID 23062647
24. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev*. Feb 11 2016;2:CD011349. PMID 26867004
25. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant role of amniotic membrane transplantation in acute ocular stevens-johnson syndrome: a randomized control trial. *Ophthalmology*. Mar 2016;123(3):484-491. PMID 26686968

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