

## Corporate Medical Policy

### Amniotic Membrane and Amniotic Fluid Injections

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**Last CAP Review:** 8/2018  
**Next CAP Review:** 8/2019  
**Last Review:** 8/2018

#### Description of Procedure or Service

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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. There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause 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, one d-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.

HAM is an established treatment for corneal reconstruction and is being evaluated for the treatment of various 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 a wide variety of conditions.

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. The fluid contains proteins, carbohydrates, proteins and 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. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricin, 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. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. .

**Related policies:**

Bioengineered Skin and Tissue  
Growth Factors in Wound Healing

# Amniotic Membrane and Amniotic Fluid Injections

Meniscal Allograft and Collagen Meniscus Implants  
Orthopedic Applications of Stem Cell Therapy  
Plugs for Fistula Repair

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

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**BCBSNC will provide coverage for human amniotic membrane when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met.**

**Injection of human amniotic fluid is considered investigational for all indications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Amniotic Membrane and Amniotic Fluid Injections are covered

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Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary:

- AmnioBand® Membrane
- Biovance®
- Epifix®
- GrafixCore™ or GrafixPrime™

NOTE: application of Epifix is limited to no more than 5 weekly applications per wound.

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

## When Amniotic Membrane and Amniotic Fluid Injections are not covered

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Sutured human amniotic membrane grafts are considered investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy.

Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is investigational.

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

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

# Amniotic Membrane and Amniotic Fluid Injections

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

## **Policy Guidelines**

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

Ulcers for individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of human amniotic membrane (HAM; AmnioBand Membrane, Biovance, Epifix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on amniotic and placental membrane products for the treatment of nonhealing diabetic lower-extremity ulcers includes several RCTs that compared HAM to standard care or to an established advanced wound care product. These industry-sponsored studies used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (AmnioBand Membrane, Biovance, Epifix, Grafix), results have shown improved outcomes compared to 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 patch or flowable formulation of HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. In a randomized comparison of a cryopreserved HAM (c-HAM) product to standard of care, there was no difference between the experimental and controls groups in complete wound closure at 4 weeks. Because HAM has not been shown to improve healing of venous ulcers in controlled studies, comparative studies on other HAM products are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Osteoarthritis**

For individuals who have knee osteoarthritis who receive injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid, the evidence includes a feasibility study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pilot study was in preparation for a larger RCT of HAM injection. Additional trials, which will have a larger sample sizes and longer follow-up, are needed to permit conclusions on the effect of this treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Plantar Fasciitis**

For individuals who have plantar fasciitis who receive injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Literature on HAM injections is at a very early stage. Evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of this treatment on plantar fasciitis pain. Also needed are RCTs in humans to evaluate the efficacy of amniotic membrane and amniotic fluid injections for the treatment of other conditions, including but not limited to tendonitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

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## **Ophthalmic Conditions**

For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, persistent epithelial defects or other ophthalmic disorders who received 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 includes 1 within-subject comparative study and case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Traditionally, amniotic membrane has been sutured onto the eye for a variety of severe ocular surface disorders. The Prokera device is novel because it has a ring around the cryopreserved HAM allograft that permits it to be inserted under topical anesthesia, similar to insertion of a contact lens, allowing for more widespread use. Use of Prokera has been reported for refractory ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency. Current evidence on use of the Prokera device is limited. While the case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs are needed to determine whether HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes. A review of the literature has shown that amniotic membrane has been used for nearly two decades for ophthalmic disorders and although RCT evidence is limited, generally accepted medical practice supports the use of sutured or glued amniotic membrane for neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: Q4131, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4177, Q4178, Q4181*

*Nonhealing is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks.*

*There are specific HCPCS codes for some of these products. If no specific HCPCS code exists for the product, an unlisted code such as Q4100 would be used.*

*There are no specific codes for AmnioFix or OrthoFlo. It is possible that it might be reported using the code for another MiMedx product such as Q4145 – Epifix, injectable, 1 mg, or the not otherwise specified code Q4100.*

*There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (e.g., 20550), the unlisted general musculoskeletal system code (20999), or if subcutaneous or intramuscular, the therapeutic injection code (96372)*

*Codes for placement of amniotic membrane on the ocular surface: 65778, 65779*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

# Amniotic Membrane and Amniotic Fluid Injections

## Scientific Background and Reference Sources

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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

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

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149. 2/11/2016

Medical Director Review 9/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 1/12/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 5/8/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 2/8/2018

## Policy Implementation/Update Information

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- 7/26/16 New policy developed. Injection of micronized amniotic membrane or amniotic fluid is considered investigational for all indications. See also policy titled "Bioengineered Skin and Tissue." (an)
- 10/25/16 Specialty Matched Consultant Advisory Panel review 9/28/2016. Policy accepted as written. (an)
- 2/24/17 Description section extensively revised. Policy statement revised: **"BCBSNC will provide coverage for human amniotic membrane when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met."** Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary: AmnioBand® Membrane, Biovance®, Epifix®, Grafix™. All other human amniotic membrane products (micronized or particulated human amniotic membrane or human amniotic fluid) for any other indications are considered investigational. Policy Guidelines section updated. Coding/Billing section updated to include codes and coding instructions. (an)
- 4/28/17 Following statement added to the When Covered section: application of Epifix is limited to no more than 5 weekly applications per wound. (This statement was moved out of the Bioengineered Skin medical policy and into this policy). (an)
- 6/30/17 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. Sutured human amniotic membrane grafts are considered investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy. Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is investigational. Policy Guidelines updated. Codes 65778, 65779 added to Billing/Coding section. Reference added. **Notification given 6/30/17 for policy effective date of 9/29/17.** (an)

# Amniotic Membrane and Amniotic Fluid Injections

- 12/15/17 Codes added to Billing/Coding section effective 1/1/2018: Q4177, Q4178, Q4181. (an)
- 3/29/18 Revised 2 statements in the “When Not Covered” to read: Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis and All other human amniotic membrane products and indications not listed above are considered investigational, including but not limited to treatment of lower extremity ulcers due to venous insufficiency. Reference added. (an)
- 9/7/18 Specialty Matched Consultant Advisory Panel review 8/22/2018. No change to policy statement. (an)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.