Amniotic Membrane and Amniotic Fluid Injections

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.

FDA REGULATORY STATUS
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Human amniotic membrane and amniotic fluid are included in these regulations.

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

Amniotic membrane grafts that are fixated using sutures or glue fixation or secured under a bandage contact lens 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

Amniotic membrane grafts using suture or glue fixation is 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.

Self-contained or unfixed amniotic membrane products (eg, Prokera®) for ophthalmic indications are considered not medically necessary.
Injection of micronized or particulated human amniotic membrane is considered investigational for all indications.

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

All other human amniotic membrane products and indications not listed above are considered investigational.

**POLICY GUIDELINES**

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

Persistent epithelial defect has 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 is defined as 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 amniotic membrane grafts (AMGs). AMG requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day.

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**RATIONALE**

**Summary of Evidence**

**Diabetic Lower-Extremity 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 (<20% healing with ≥2 weeks of standard care) 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.

Ophthalmic Conditions

For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens Johnson, or persistent epithelial defects who receive fixated (sutured, glued or secured under a bandage contact lens) human amniotic membrane graft the evidence includes several RCTs and a technology assessment. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The most widely studied condition with a technology assessment of RCT evidence is use of HAM following pterygium repair. The technology assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT on HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to conventional therapy. One RCT has shown that application of c-HAM in the early stages of Stevens Johnson leads to clinically significant improvement compared to medical therapy alone. Other indications have been studied only in case series. RCTs are needed to evaluate the efficacy of this procedure. 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, or persistent epithelial defects who receive fixated (sutured, glued or secured under a bandage contact lens) human amniotic membrane graft, the evidence includes 2 RCTs and a systematic review of 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A 2012 Cochrane review found a single RCT on HAM graft for acute ocular burns. The study suggested a benefit on rate of healing for ocular burns but the study was considered to be at high or uncertain risk of bias due to unequal baseline scores and the lack of masking to treatment condition. A study on HAM for the treatment of bullous keratopathy reported that that there was no difference in clinical outcomes between HAM and stromal puncture. RCTs are needed for the benefit of HAM for these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic conditions who receive an self-retained or unfixed formulation of HAM, the evidence includes one 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 by having a ring around the c-HAM allograft that allows 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 report generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens when used for wound healing after PRK. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
**FEP 7.01.149 Amniotic Membrane and Amniotic Fluid Injections**

### POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>January 2017</td>
<td>New Policy</td>
<td>Policy updated with literature review through November 7, 2016; material on patch formulations of amniotic membrane moved from policy 7.01.113 (Bioengineered Skin and Soft Tissue Substitutes); references 7-8, 15, 18, 20, and 22-23 added. AmnioBand® Membrane, Biovance®, Epifix®, Grafix™ considered medically necessary for diabetic foot ulcers; all other products and indications are investigational.</td>
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<tr>
<td>June 2017</td>
<td>Revise Policy</td>
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