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Medical Benefit		Effective Date: 07/01/18	Next Review Date: 03/19
Preauthorization	Yes	Review Dates: 03/17, 03/18	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With nonhealing diabetic lower-extremity ulcers	Interventions of interest are: • Patch or flowable formulation of human amniotic membrane	Comparators of interest are: • Standard wound care • Advanced wound therapies	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With lower-extremity ulcers due to venous insufficiency	Interventions of interest are: • Patch or flowable formulation of human amniotic membrane	Comparators of interest are: • Compression therapy • Advanced wound therapies	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With knee osteoarthritis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With plantar fasciitis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects	Interventions of interest are: • Sutured human amniotic membrane graft	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects 	Interventions of interest are: <ul style="list-style-type: none"> • Sutured human amniotic membrane graft 	Comparators of interest are: <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: <ul style="list-style-type: none"> • With ophthalmic conditions 	Interventions of interest are: <ul style="list-style-type: none"> • Human amniotic membrane without suture 	Comparators of interest are: <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life

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.

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of HAM (i.e., 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 RCTs evaluating amniotic and placental membrane products for the treatment of nonhealing (less than 20% healing with two weeks or more of standard care) diabetic lower-extremity ulcers have compared HAM to 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 analysis. For the HAM products that have been sufficiently evaluated (i.e., 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 two RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of venous lower extremity ulcers includes two multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at four weeks, but the percentage of patients with complete wound closure did not differ between EpiFix and standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but interpretation is limited by methodologic concerns. Well designed and well conducted RCTs that compare HAM with standard care for venous insufficiency ulcers 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 HAM 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 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 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 HAM or amniotic fluid, the evidence includes two small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Research on HAM injections for plantar fasciitis is at an early stage. The evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of two 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 HAM and amniotic fluid injections on plantar fasciitis pain. 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 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 the use of HAM following pterygium repair. The technology assessment concluded, based on four RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT evaluating HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to conventional therapy. 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 includes two RCTs and a systematic review that included one 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 trial suggested a benefit in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and the lack of masking of the treatment condition. A trial assessing HAM for the treatment of bullous keratopathy reported no difference in clinical outcomes between HAM and stromal puncture. RCTs are needed to evaluate 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 HAM without suture, the evidence includes an RCT (N=20), a 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 dry eye syndrome, 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 its use is limited. While the small RCT and 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 sutureless HAM improves

healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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.

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 (e.g., 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.

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

Nonhealing is defined as less than a 20% decrease in wound area with standard wound care for at least two weeks, based on the entry criteria for clinical trials (e.g., Zelen et al, 2015).

A persistent epithelial defect is one that failed to close completely after five days of conservative treatment or has failed to demonstrate a decrease in size after two 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 human amniotic membrane grafts (AMGs). An AMG requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regarding treatments requiring multiple drops per day.

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 (see Table 1).

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 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 dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.²

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures.¹ Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

Amniotic Fluid

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea.¹ The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927.³ Amniotic fluid has been compared with synovial fluid, containing hyaluronan, 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.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 the Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow) Protocol.

Table 1. Amniotic Membrane and Amniotic Fluid Preparations: Preparation and Components

Product (Supplier)	Preparation Cryopreserved, Dehydrated, or Extracted	Components			
		Amnion	Chorion	Amniotic Fluid	Umbilical Cord
Patch					
Affinity™ (NuTech Medical)	C	X			
AlloWrap™ (AlloSource)	NS	X			
AmbioDisk® (IOP Ophthalmics)	D				
AmbioDry5® (IOP Ophthalmics)	D				
AmnioBand® Membrane (MTF Wound Care)	D	X	X		
AmnioClear™ (Liventa Bioscience)	NS	X	X		
AmnioExcel® (Derma Sciences)	D	X			
AmnioFix® (MiMedx)	D	X			
AmnioGraft® (BioTissue)	C	X			
Artacent® Wound (Tides Medical)	D	X			
BioDDryFlex® (BioD)	D	X			
BioDfence™ (BioD)	D	X	X		

Product (Supplier)	Preparation Cryopreserved, Dehydrated, or Extracted	Components			
		Amnion	Chorion	Amniotic Fluid	Umbilical Cord
BioSkin (HRT) ^a	D	X	X		
Biovance® (Alliqua Biomedical)	D	X			
Clarix® (Amnio Medical)	C	X			X
Cygnus (Vivex Biomedical)	D	X			
Cygnus Max (Vivex Biomedical)	D				X
EpiCord™ (MiMedx)	D				X
EpiFix® (MiMedx)	D	X	X		
Dermavest™ (Aedicell) ^a	C	X	X		X
Grafix® (Osiris)	C	X	X		
Guardian/AmnioBand® (MTF Wound Care)	D	X	X		
Neox® 100 (Amnio Medical)	C	X			X
Neox® Cord (Amnio Medical)	C	X			X
Neox® Wound Allograft (Amnio Medical)	C	X			X
NuShield™ (NuTech Medical)	D	X	X		
PalinGen® Membrane (Amnio ReGen Solutions)	C	X			
Plurivest™ (Aedicell) ^a	C	X	X		X
Prokera® (Bio-Tissue)	C				
Revitalon™ (Medline Industries)	D	X	X		
WoundEx® (Skye Biologics) ^a	D	X	X		
Suspension, particulate, or extraction					
AmnioBand® Particulate (MTF Wound Care)	D	X	X		
AmnioMatrix® (Derma Sciences)	D	X		X	
AmnioVisc™ (Lattice Biologics)	NS			X	
BioSkin® Flow (HRT) ^b	E	X	X	X	X
Clarix® Flo (Amnio Medical)	C	X			X
Interfyl™ (Alliqua Biomedical)	NS	X	X		
Neox® Flo (Amnio Medical)	C	X			X
OrthoFlo™ (MiMedx)	D			X	
PalinGen® Flow (Amnio ReGen Solutions)	C	X		X	
PalinGen® SportFlow (Amnio ReGen Solutions)	C	X		X	
ProMatrX™ ACF (Amnio ReGen Solutions)	C	X		X	
ReNu™ (NuTech Medical)	D	X		X	
WoundEx® Flow (Skye Biologics) ^b	E	X	X	X	X

C: cryopreserved; D: dehydrated; E: extracted connective tissue; HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation; NS: not specified.

^{a, b} Processed by HRT and marketed by under different tradenames.

AmnioClip (FORTECH GmbH) is a ring designed to hold amniotic membrane in the eye without sutures or glue fixation. A mounting device is used to secure the amniotic membrane within the AmnioClip. The AmnioClip currently has CE approval in Europe.

Regulatory Status

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

In 2003, Prokera™ was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). 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.”⁴

Related Protocols

Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

Bioengineered Skin and Soft Tissue Substitutes

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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