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

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 ophthalmic conditions	Interventions of interest are: • Patch formulation of human amniotic membrane	Comparators of interest are: • Medical therapy	Relevant outcomes include: • 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 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 (less than 20% healing with two or less 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 four 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 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 two 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 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 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 ophthalmic conditions who receive patch formulation of HAM, the evidence includes RCTs 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. Results from two recent RCTs have suggested benefit, but additional study in a larger number of subjects is

needed to demonstrate consistent effects. 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. Current evidence on use of the Prokera device includes case reports and case series. Results are generally positive, but controlled studies are needed. 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**.

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 two weeks.

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 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.²

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 (see also the Bioengineered Skin and Soft Tissue Substitutes Protocol).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 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.¹ 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 1927.³ 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			
AmnioBand® Membrane (MTF Wound Care)	D	X	X		
AmnioClear™ (Liventia Bioscience)	NS	X	X		
AmnioExcel® (Derma Sciences)	D	X			
AmnioFix® (MiMedx)	D	X			
AmnioGen™ 45 (US Biologix) ^a	D	X			
AmnioGen™ 200 (US Biologix) ^a	D		X		
AmnioGraft® (BioTissue)	C	X			
AmnioPro® 45 (HRT) ^a	D	X			X
AmnioPro® 200 (HRT) ^a	D		X		X
Artacent® Wound (Tides Medical)	D	X			
BioDDryFlex® (BioD)	D	X			
BioDfence™ (BioD)	D	X	X		
BioRenew 45 (HRT) ^a	D	X			
BioRenew 200 (HRT) ^a	D		X		
BioSkin (thin) (HRT) ^a	D	X			
BioSkin (thick) (HRT) ^a	D		X		
Biovance® (Aliqual 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		
HydraTek® (Human Regenerative Technologies)	D	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
Revitalon™ (Medline Industries)	D	X	X		
WoundEx® 45 (Skye Biologics) ^a	D	X			

Product (Supplier)	Preparation Cryopreserved, Dehydrated, or Extracted	Components			
		Amnion	Chorion	Amniotic Fluid	Umbilical Cord
WoundEx® 200 (Skye Biologics) ^a	D		X		
Suspension, particulate, or extraction					
AmnioBand® Particulate (MTF Wound Care)	D	X	X		
AmnioGen™-A (US Biologix) ^b	E	X	X	X	X
AmnioGen™-C (US Biologix) ^b	C	X	X	X	X
AmnioMatrix® (Derma Sciences)	D	X		X	
AmnioPro® Flow (HRT) ^b	E	X	X	X	X
AmnioVisc™ (Lattice Biologics)	NS			X	
BioRenew® Flow (HRT) ^b	E	X	X	X	X
BioSkin® Flow (HRT) ^b	E	X	X	X	X
Clarix® Flo (Amnio Medical)	C	X			X
HydraTek® (Human Regenerative Technologies)	D	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.

The preferred outcomes for the healing of lower-extremity ulcers and burn wounds are the percentage of patients with complete wound healing and the time to complete wound healing.⁴ The percentage of patients with 50% wound healing and time to 50% wound healing have also been considered appropriate outcomes for these conditions.⁵ The percent change in wound area at four weeks is predictive of complete healing at 12 weeks in patients with diabetic foot ulcers.⁶ Thus, minimal improvement at 30 days can be considered as an indicator that a wound is unlikely to heal in patients with comorbidities known to affect wound healing, but would not be considered a primary outcome measure.

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.

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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