

(701149)

Medical Benefit		Effective Date: 06/01/19	Next Review Date: 03/21
Preauthorization	Yes	Review Dates: 03/17, 03/18, 03/19, 03/20	

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: <ul style="list-style-type: none"> With nonhealing diabetic lower-extremity ulcers 	Interventions of interest are: <ul style="list-style-type: none"> Patch or flowable formulation of human amniotic membrane 	Comparators of interest are: <ul style="list-style-type: none"> Standard wound care Advanced wound therapies 	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 lower-extremity ulcers due to venous insufficiency 	Interventions of interest are: <ul style="list-style-type: none"> Patch or flowable formulation of human amniotic membrane 	Comparators of interest are: <ul style="list-style-type: none"> Compression therapy Advanced wound therapies 	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 knee osteoarthritis 	Interventions of interest are: <ul style="list-style-type: none"> Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid 	Comparators of interest are: <ul style="list-style-type: none"> Conservative therapy Corticosteroid injections 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Functional outcomes Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With plantar fasciitis 	Interventions of interest are: <ul style="list-style-type: none"> Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid 	Comparators of interest are: <ul style="list-style-type: none"> Conservative therapy Corticosteroid injections 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Functional outcomes Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative treatment, OR corneal ulcers and melts that do not respond to initial medical therapy 	Interventions of interest are: <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane 	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

Populations	Interventions	Comparators	Outcomes
<p>Individuals:</p> <ul style="list-style-type: none"> • With corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment OR with bullous keratopathy as a palliative measure in patients who are not candidates for a curative treatment (e.g., endothelial or penetrating keratoplasty) 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured or self-retained human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
<p>Individuals:</p> <ul style="list-style-type: none"> • With partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient OR with moderate or severe Stevens-Johnson syndrome 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured or self-retained human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
<p>Individuals:</p> <ul style="list-style-type: none"> • With persistent epithelial defects that do not respond to conservative therapy OR with severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured or self-retained human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
<p>Individuals:</p> <ul style="list-style-type: none"> • With moderate or severe acute ocular chemical burn 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured or self-retained human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
<p>Individuals:</p> <ul style="list-style-type: none"> • With corneal perforation when corneal tissue is not immediately available 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life
<p>Individuals:</p> <ul style="list-style-type: none"> • With pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Sutured or glued human amniotic membrane 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Medical therapy • Bandage contact lens 	<p>Relevant outcomes include:</p> <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 non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (i.e., AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes randomized controlled trials (RCTs). The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life (QOL). The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with two weeks or more of standard care) diabetic lower-extremity ulcers have compared HAM with 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, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with 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 a patch or flowable formulation of HAM, the evidence includes two RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of lower-extremity venous 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 the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the standard of 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 an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. The relevant outcomes are symptoms, functional outcomes, QOL, 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

The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (n=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in the Visual Analog Score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an interim report with 12-month results pending. The evidence is insufficient to determine the effects of the technology on health outcomes.

OPHTHALMIC CONDITIONS

Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Ulcers and Melts That Does Not Respond to Initial Medical Therapy

For individuals who have corneal ulcers and melts that does not respond to initial medical therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Bullous Keratopathy as a Palliative Measure in Patients Who are not Candidates for a Curative Treatment (e.g., endothelial or penetrating keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient

For individuals who have partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Stevens-Johnson Syndrome

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of Stevens-Johnson includes one RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease supported the use of HAM for moderate or severe Stevens-Johnson syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Persistent Epithelial Defects and Ulceration That Do Not Respond to Conservative Therapy

For individuals who have persistent epithelial defects that do not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulcerations that do not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Severe Dry Eye with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for two to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as three months. Clinical input supported HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pteryg-

ium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (e.g., extensive, double, or recurrent pterygium). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

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

Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) may be considered **medically necessary** for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see Policy Guidelines);
- Corneal ulcers and melts that do not respond to initial conservative therapy (see Policy Guidelines);
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
- Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty);
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;
- Moderate or severe Stevens-Johnson syndrome;
- Persistent epithelial defects that do not respond to conservative therapy (See Policy Guidelines);
- Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue may be considered **medically necessary** for the treatment of the following ophthalmic indications:

- Corneal perforation when corneal tissue is not immediately available; or
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Human amniotic membrane with or without suture are considered **investigational** for all indications not outlined above.

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 of diabetic wounds 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).

TEAR FILM AND OCULAR SURFACE SOCIETY STAGED MANAGEMENT FOR DRY EYE DISEASE (JONES ET AL, 2017)

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:

If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

Step 4:

If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

DRY EYE SEVERITY LEVEL DEWS 3 TO 4

Discomfort, severity, and frequency - Severe frequent or constant

Visual symptoms - chronic and/or constant, limiting to disabling

Conjunctival Injection - +/- or +/+

Conjunctive Staining - moderate to marked

Corneal Staining - marked central or severe punctate erosions

Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris

Lid/meibomian glands - Frequent

Tear film breakup time - <5

Schirmer score (mm/5 min) - <5

BACKGROUND

HUMAN AMNIOTIC MEMBRANE

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).

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.¹ There is evidence that the tissue has anti-inflammatory, anti-fibroblastic, 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, 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, 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.

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	Components			
		Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid
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® (Bio-Tissue)	C	X			
Artacent® Wound (Tides Medical)	D	X			
BioDDryFlex® (BioD)	D	X			
BioDfence™ (BioD)	D	X	X		
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

Product (Supplier)	Preparation	Components			
		Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid
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.

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, 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 Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The Food and Drug Administration 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 The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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

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 and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services 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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