BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 7.01.149 Amniotic Membrane and Amniotic Fluid

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Related Policies:

7.01.113 - Bioengineered Skin and Soft Tissue Substitutes
8.01.52 - Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Amniotic Membrane and Amniotic Fluid

Description

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.

OBJECTIVE

The objective of this evidence review is to evaluate whether various human amniotic membrane products improve the net health outcome for individuals with various diabetic and venous ulcers, osteoarthritis, plantar fasciitis, and ophthalmic conditions.

POLICY STATEMENT

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

Human amniotic membrane grafts with or without suture 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;
- Corneal ulcers and melts that do not respond to initial conservative therapy;
- 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 (eg, 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 within 2 days to conservative therapy;
- 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 grafts with or without suture are considered **investigational** for all ophthalmic 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 uses reviewed herein of the human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **investigational** (see Policy Guidelines).

All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) including but not limited to those in Table PG2 (see Policy Guidelines) for indications not listed above are considered **investigational** for indications reviewed herein, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.

POLICY GUIDELINES

Non-healing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks, based on the entry criteria for clinical trials (eg, Zelen et al [2015]).

Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022]).

This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code.

Table PG1. Amniotic Products Listed in the Policy Statements

Trade Name	Supplier	HCPCS Code
Affinity	Organogenesis (previously NuTech Medical)	Q4159
AmnioBand Membrane	MTF Wound Care	Q4151
AmnioExcel	Integra	Q4137
Biovance	Celularity	Q4154
Epifix	MiMedx	Q4186
Epicord	MiMedx	Q4187
Grafix	Osiris	Q4132, Q4133

Table PG2. Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
AlloGen	Vivex Biomedical	Q4212
AlloWrap™	AlloSource	Q4150
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™	Tissue Transplant Technology	Q4188
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™	Stability Biologics	Q4227
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235
Amniotext patch	Regenerative Labs	Q4247
AmnioWrap2™	Direct Biologics	Q4221
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190

Artacent Wound	Tides Medical	Q4169
Ascent	StimLabs	Q4213
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
BioDDryFlex	BioD	Q4138
BioDfence™	Integra Life Science	Q4140
BioNextPATCH	BioNext Solutions	Q4228
BioWound, BioWound Plus™, BioWound XPlus™	HRT[a]	Q4217
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
Clarix	Amniox Medical	Q4156
Clarix Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170
Dermacyte	Merakris Therapeutics	Q4248
Dermavest™ or Plurivest	AediCell[a]	Q4153
Derm-maxx	Royal Biologics	Q4238
Epifix Injectable	MiMedx	Q4145
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Guardian/AmnioBand	MTF Wound Care	Q4151
Interfyl	Celularity	Q4171

Matrion	LifeNet Health	Q4201
Neopatch or Therion	CryoLife	Q4176
Neox Cord	Amniox Medical	Q4148
Neox Flo	Amniox Medical	Q4155
Neox Wound	Amniox Medical	Q4156
Restorigin	UMTB Biomedical	Q4191
Novafix	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuShield	Organogenesis	Q4160
PalinGen Membrane	Amnio ReGen Solutions	Q4173
PalinGen SportFlow	Amnio ReGen Solutions	Q4174
Plurivest™	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4244
Reguard	New Life Medical	Q4255
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™	Medline Industries	Q4157
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT™	Synergy Biologics	Q4183
WoundEx	Skye Biologics[a]	Q4163
WoundEx Flow	Skye Biologics[a]	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation

[a] Processed by HRT and marketed under different tradename

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 (eg 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

BENEFIT APPLICATION

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

None

FDA 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. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[4,]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer"s objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
    1. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    2. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        1. Is for autologous use;
        2. Is for allogeneic use in a first-degree or second-degree blood relative; or
        3. Is for reproductive use."

The guidance provides the following specific examples of homologous and non-homologous use for amniotic membrane:

1. "Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.
2. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.
3. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane."

The FDA noted the intention to exercise enforcement discretion for the next 36 months after publication of the guidance.

In 2003, Prokera was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104; product code: NQB). 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."[5,] The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

RATIONALE

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a formulation of human amniotic membrane (HAM) or placental membrane (ie, Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, 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 non-healing (<20% healing with ≥2 weeks 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 (ie, Affinity, 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 an 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 formulation of HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix and 1 multicenter RCT with Amnioband. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. The third RCT demonstrated significantly greater blinded assessor-confirmed rates of complete wound closure at 12 weeks after weekly or twice-weekly application of AmnioBand Membrane with compression bandaging compared with compression bandaging alone. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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. 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 that the technology results in an improvement in the net health outcome.

Plantar Fasciitis

For individuals who have plantar fasciitis who receive an injection of amniotic membrane, the evidence 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 that the technology results in an improvement in the net health outcome.

Ophthalmic Conditions

Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have corneal ulcers and melts, that do not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-randomized comparative study. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. The systematic review showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative evidence was identified for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Bullous Keratopathy as a Palliative Measure in Patients Who are Not Candidates for a Curative Treatment (eg, Endothelial or Penetrating Keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials 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. The evidence is insufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome (includes 1 RCT with 25 patients [50 eyes]) found improved symptoms and function with HAM compared to medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on persistent epithelial defects and ulceration. The evidence is insufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in an 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 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The standard treatment for corneal perforation is corneal transplantation, however, HAM may provide temporary coverage of the severe defect when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 pterygium recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Repair Following Mohs Micrographic Surgery

For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amnionic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of patients requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (p<.0001). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Society for Vascular Surgery et al.

In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."[41,]

Tear Film and Ocular Surface Society

In 2017, the Tear Film and Ocular Surface Society published the Dry Eye Workshop II (DEWS) management and therapy report.[24,] The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

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 (eg tarsorrhaphy, salivary gland transplantation)

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[42,] The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, "healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed." References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES

1. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine?. Regen Med. Mar 2009; 4(2): 275-91. PMID 19317646
2. 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
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(I):167-177.
4. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. 2017 https://www.regulations.gov/document?D=FDA-2017-D-6146-0003 Accessed January 3, 2024
5. Food and Drug Administration. 510(k) Summary: ProKeraTM Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed January 3, 2024.
6. Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. J Comp Eff Res. Jan 2020; 9(1): 23-34. PMID 31691579
7. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. Wound Repair Regen. May 2018; 26(3): 274-283. PMID 30098272
8. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. Feb 2019; 16(1): 122-130. PMID 30246926
9. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. Dec 2018; 15(6): 950-957. PMID 30019528
10. Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds. Mar 2016; 28(3): 70-7. PMID 26978860
11. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. Dec 2015; 12(6): 724-32. PMID 25424146

12. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. Apr 2016; 13(2): 272-82. PMID 26695998
13. Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. Feb 2019; 16(1): 19-29. PMID 30136445
14. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix() for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. Oct 2014; 11(5): 554-60. PMID 25048468
15. Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. Jun 2015; 27(6): 158-69. PMID 26061491
16. Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. Int Wound J. Jun 2017; 14(3): 569-577. PMID 27489115
17. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014; 22(6): 688-93. PMID 25224019
18. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix) allograft for the treatment of venous leg ulcers. Int Wound J. Feb 2018; 15(1): 114-122. PMID 29024419
19. Bianchi C, Tettelbach W, Istwan N, et al. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. Jun 2019; 16(3): 761-767. PMID 30864259
20. Serena TE, Orgill DP, Armstrong DG, et al. A Multicenter, Randomized, Controlled, Clinical Trial Evaluating Dehydrated Human Amniotic Membrane in the Treatment of Venous Leg Ulcers. Plast Reconstr Surg. Nov 01 2022; 150(5): 1128-1136. PMID 36067479
21. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. Aug 2016; 29(6): 443-50. PMID 26683979
22. Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. Br J Sports Med. Nov 2016; 50(22): 1367-1375. PMID 27143138
23. 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): 1332-9. PMID 23945520
24. Cazzell S, Stewart J, Agnew PS, et al. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. Foot Ankle Int. Oct 2018; 39(10): 1151-1161. PMID 30058377
25. Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. Eye Contact Lens. Sep 2013; 39(5): 341-7. PMID 23945524
26. Liu J, Li L, Li X. Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis. Cornea. Apr 2019; 38(4): 454-462. PMID 30702468
27. Yin HY, Cheng AMS, Tighe S, et al. Self-retained cryopreserved amniotic membrane for treating severe corneal ulcers: a comparative, retrospective control study. Sci Rep. Oct 12 2020; 10(1): 17008. PMID 33046729
28. Paris Fdos S, Gonalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. Aug 2013; 97(8): 980-4. PMID 23723410
29. Kheirkhah A, Casas V, Raju VK, et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am J Ophthalmol. May 2008; 145(5): 787-94. PMID 18329626
30. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. Eye Contact Lens. Jul 2009; 35(4): 172-5. PMID 19474753
31. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens-Johnson Syndrome: A Randomized Control Trial. Ophthalmology. Mar 2016; 123(3): 484-91. PMID 26686968
32. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. Ocul Surf. Jul 2004; 2(3): 201-11. PMID 17216092
33. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 2017: 6404918. PMID 28894606
34. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328
35. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. Feb 2011; 95(2): 199-204. PMID 20675729
36. Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial. Am J Ophthalmol. Mar 2019; 199: 209-215. PMID 30419194
37. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. Nov 2005; 112(11): 1963-9. PMID 16198422
38. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. Ophthalmology. Jan 2013; 120(1): 201-8. PMID 23062647
39. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. Feb 11 2016; 2(2): CD011349. PMID 26867004
40. Toman J, Michael GM, Wisco OJ, et al. Mohs Defect Repair with Dehydrated Human Amnion/Chorion Membrane. Facial Plast Surg Aesthet Med. 2022; 24(1): 48-53. PMID 34714143

41. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. Feb 2016; 63(2 Suppl): 3S-21S. PMID 26804367
42. Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2016; 24(1): 112-26. PMID 26663430

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
January 2017	New Policy	
March 2017	Replace policy	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. .
June 2017	Replace policy	Policy updated with literature review through April 27, 2017; references 21-28 added. Clinical input reviewed. Fixated amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens Johnson, and persistent epithelial defects.
March 2018	Replace policy	Policy updated with literature review through December 11, 2017; references 15, 22, and 27 added. Specific indications added to the investigational policy statements.
June 2019	Replace policy	Policy updated with literature review through November 27, 2018; references added. Clinical input reviewed. EpiCord add to medically necessary statement for diabetic lower extremity ulcers. Sutured and non-sutured amniotic membrane may be considered medically necessary for specified ophthalmic conditions.
June 2020	Replace policy	Policy updated with literature review through December 20, 2019; references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through December 28, 2020; references added. Affinity added to medically necessary statement for the treatment of diabetic foot ulcers; edits made to investigational statement on human amniotic products.
June 2022	Replace policy	Policy updated with literature review through January 3, 2022; references added. New indication and investigational statement added for treatment following Mohs microsurgery.
June 2023	Replace policy	Policy updated with literature review through January 20, 2023; no references added. Policy statements unchanged.
June 2024	Replace policy-Corrections only	Corrections made to Table PG2: Edited trade name and supplier for code Q4191 (Restorigin, UMTB Biomedical); deleted code Q4126 (code was moved to policy 7.01.113).