MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Amniotic Membrane and Amniotic Fluid

Table of Contents

Policy Number: 643

BCBSA Reference Number: 7.01.149
NCD/LCD: NA

Related Policies

- Recombinant and Autologous Platelet-Derived Growth Factors for Healing and Other Non–Orthopedic Conditions, #186
- Bioengineered Skin and Soft Tissue Substitutes, #663
- Orthopedic Applications of Stem Cell Therapy, #254

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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

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

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 (eg, 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.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
Q4132	Grafix core and grafixpl core, per square centimeter
Q4133	Grafix prime, grafixpl prime, stravix and stravixpl, per square centimeter
Q4151	Amnioband or guardian, per square centimeter
Q4154	Biovance, per square centimeter
Q4168	Amnioband, 1 mg
Q4186	Epifix, per square centimeter

The following ICD Diagnosis Codes are considered medically necessary when submitted with the HCPCS codes above if medical necessity criteria are met:

ICD-10 Diagnosis Coding

ICD-10-CM-diagnosis codes:	Code Description
E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E08.622	Diabetes mellitus due to underlying condition with other skin ulcer
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E09.622	Drug or chemical induced diabetes mellitus with other skin ulcer
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer
E13.621	Other specified diabetes mellitus with foot ulcer
E13.622	Other specified diabetes mellitus with other skin ulcer

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured

The following ICD Diagnosis Codes are considered medically necessary when submitted with the HCPCS codes above if medical necessity criteria are met:

ICD-10 Diagnosis Coding

ICD-10-CM-diagnosis codes:	Code Description
H11.001	Unspecified pterygium of right eye
H11.002	Unspecified pterygium of left eye
H11.003	Unspecified pterygium of eye, bilateral
H11.009	Unspecified pterygium of unspecified eye
H11.011	Amyloid pterygium of right eye
H11.012	Amyloid pterygium of left eye
H11.013	Amyloid pterygium of eye, bilateral
H11.019	Amyloid pterygium of unspecified eye
H11.021	Central pterygium of right eye
H11.022	Central pterygium of left eye
H11.023	Central pterygium of eye, bilateral
H11.029	Central pterygium of unspecified eye
H11.031	Double pterygium of right eye
H11.032	Double pterygium of left eye
H11.033	Double pterygium of eye, bilateral
H11.039	Double pterygium of unspecified eye
H11.041	Peripheral pterygium, stationary, right eye
H11.042	Peripheral pterygium, stationary, left eye
H11.043	Peripheral pterygium, stationary, bilateral
H11.049	Peripheral pterygium, stationary, unspecified eye
H11.051	Peripheral pterygium, progressive, right eye
H11.052	Peripheral pterygium, progressive, left eye

H11.053	Peripheral pterygium, progressive, bilateral
H11.059	Peripheral pterygium, progressive, unspecified eye
H11.061	Recurrent pterygium of right eye
H11.062	Recurrent pterygium of left eye
H11.063	Recurrent pterygium of eye, bilateral
H11.069	Recurrent pterygium of unspecified eye
H16.001	Unspecified corneal ulcer, right eye
H16.002	Unspecified corneal ulcer, left eye
H16.003	Unspecified corneal ulcer, bilateral
H16.009	Unspecified corneal ulcer, unspecified eye
H16.011	Central corneal ulcer, right eye
H16.012	Central corneal ulcer, left eye
H16.013	Central corneal ulcer, bilateral
H16.019	Central corneal ulcer, unspecified eye
H16.021	Ring corneal ulcer, right eye
H16.022	Ring corneal ulcer, left eye
H16.023	Ring corneal ulcer, bilateral
H16.029	Ring corneal ulcer, unspecified eye
H16.031	Corneal ulcer with hypopyon, right eye
H16.032	Corneal ulcer with hypopyon, left eye
H16.033	Corneal ulcer with hypopyon, bilateral
H16.039	Corneal ulcer with hypopyon, unspecified eye
H16.041	Marginal corneal ulcer, right eye
H16.042	Marginal corneal ulcer, left eye
H16.043	Marginal corneal ulcer, bilateral
H16.049	Marginal corneal ulcer, unspecified eye
H16.051	Mooren's corneal ulcer, right eye
H16.052	Mooren's corneal ulcer, left eye
H16.053	Mooren's corneal ulcer, bilateral
H16.059	Mooren's corneal ulcer, unspecified eye
H16.061	Mycotic corneal ulcer, right eye
H16.062	Mycotic corneal ulcer, left eye
H16.063	Mycotic corneal ulcer, bilateral
H16.069	Mycotic corneal ulcer, unspecified eye
H16.071	Perforated corneal ulcer, right eye
H16.072	Perforated corneal ulcer, left eye
H16.073	Perforated corneal ulcer, bilateral
H16.079	Perforated corneal ulcer, unspecified eye
H16.231	Neurotrophic keratoconjunctivitis, right eye
H16.232	Neurotrophic keratoconjunctivitis, left eye
H16.233	Neurotrophic keratoconjunctivitis, bilateral
H16.239	Neurotrophic keratoconjunctivitis, unspecified eye
H18.831	Recurrent erosion of cornea, right eye
H18.832	Recurrent erosion of cornea, left eye
H18.833	Recurrent erosion of cornea, bilateral
H18.839	Recurrent erosion of cornea, unspecified eye
L51.1	Stevens-Johnson syndrome

The following CPT and HCPCS codes are considered investigational for <u>Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:</u>

CPT Codes

CPT codes:	Code Description
65778	Placement of amniotic membrane on the ocular surface; without sutures

HCPCS Codes

HCPCS codes:	Code Description
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
Q4138	Biodfence dryflex, per square centimeter
Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4140	Biodfence, per square centimeter
Q4145	EpiFix, injectable, 1 mg
Q4148	Neox cord 1k, neox cord rt, or clarix cord 1k, per square centimeter
Q4150	Allowrap ds or dry, per square centimeter
Q4153	Dermavest and plurivest, per square centimeter
Q4155	NeoxFlo or ClarixFlo, 1 mg
Q4156	Neox 100 or clarix 100, per square centimeter
Q4157	Kerecis omega3, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	Nushield, per square centimeter
Q4162	Woundex flow, bioskin flow, 0.5 cc
Q4163	Woundex, bioskin, per square centimeter
Q4169	Artacent wound, per square centimeter
Q4170	Cygnus, per square centimeter
Q4171	Interfyl, 1 mg
Q4173	Palingen or palingen xplus, per square centimeter
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4176	Neopatch, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	Floweramniopatch, per square centimeter
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio Wound, per sq cm
Q4183	Surgigraft, per square centimeter
Q4184	Cellesta, per square centimeter
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4187	Epicord, per square centimeter
Q4188	Amnioarmor, per square centimeter
Q4189	Artacent ac, 1 mg
Q4190	Artacent ac, per square centimeter
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4194	Novachor, per square centimeter
Q4198	Genesis amniotic membrane, per square centimeter
Q4201	Matrion, per square centimeter
Q4204	Xwrap, per square centimeter

Description

HUMAN AMNIOTIC MEMBRANE

Human amniotic membrane (HAM) consists of 2 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, antifibroblastic, 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, 1 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 policy #254.

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

Product (Supplier)	Preparation	Components			
	Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid	Umbilical Cord
Patch					
Affinity™ (NuTech Medical)	C	X			
AlloWrap™ (AlloSource)	NS	X			
AmbioDisk (IOP Ophthalmics)	D				
AmbioDry2 (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		
BioSkin (HRT)a	D	X			
Biovance® (Aliqual Biomedical)	D	X			
Clarix® (Amniox 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 (Amniox Medical)	C	X			X
Neox® Cord (Amniox Medical)	C	X			X
Neox® Wound Allograft (Amniox 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® (45 microns, Skye Biologics)a	D	X			
WoundEx® (200 microns, Skye Biologics)a	D		X		
Suspension, particulate, or extraction					
AmnioBand® Particulate (MTF Wound Care)	D	X	X	X	
AmnioMatrix® (Derma Sciences)	D	X		X	
AmnioVisc™ (Lattice Biologics)	NS				X
BioSkin® Flow (HRT)b	E	X	X	X	
Clarix® Flo (Amniox Medical)	C	X	X		X
Interfyl™ (Alliqua Biomedical)	NS	X	X		
Neox® Flo (Amniox 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.

Summary

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.

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (ie, 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 (<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, AmnioBand Membrane, Biovance, 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 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of lower-extremity venous ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at 4 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. 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 an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes 2 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 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of 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 4 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 a systemic review article and RCTs. 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 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 with 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.

Clinical input obtained in 2017 supports that the following indications provide a clinically meaningful improvement in net health outcome and are consistent with generally accepted medical practice.

- Use of sutured human amniotic membrane (also described as amniotic membrane graft [AMG]) for individuals with:
    - Neurotrophic keratitis
    - Corneal ulcers and melts
    - Following pterygium repair
    - Stevens-Johnson syndrome, and
    - Persistent epithelial defects.

Thus, the above indications may be considered medically necessary considering the suggestive evidence and clinical input support.

However, the clinical input does not support whether the following indications provide a clinically meaningful improvement in the net health outcome or are consistent with generally accepted medical practice.

- Use of sutured AMG for individuals with
- Corneal perforation
- Bullous keratopathy

- Limbus stem cell deficiency, and
- Severe dry eye.

Thus, the above indications may be considered investigational.

The clinical input also does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:
- Use of sutureless AMG (eg, Prokera) instead of sutured AMG.

Thus, the above indication may be considered investigational.

Policy History

Date	Action
1/2019	Clarified coding information.
7/2018	BCBSA National medical policy review. Investigational indications added. Clarified coding information. Effective 7/1/2018.
1/2018	Clarified coding information.
10/2017	BCBSA National medical policy review. New medically necessary and investigational indications described. Ophthalmic products added and discontinued product names removed from Table 1. Clarified coding information. Effective 10/1/2017.
6/2017	BCBSA National medical policy. New medically necessary and investigational indications described. Clarified coding information. Effective 6/1/2017.
9/2015	New medical policy describing investigational indications. Effective 9/1/2015.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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):275-291. 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. PMID
4. Food and Drug Administration. 510(k) Summary: ProKera™ Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed January 26, 2018.
5. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open.* Oct 2016;4(10):e1095. PMID 27826487
6. 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):70-77. PMID 26978860
7. Smiell JM, Treadwell T, Hahn HD, et al. Real-world experience with a decellularized dehydrated human amniotic membrane allograft. *Wounds.* Jun 2015;27(6):158-169. PMID 26061491

8. Zelen CM, Serena TE, Denoziere G, et al. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J.* Oct 2013;10(5):502-507. PMID 23742102
9. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long term follow-up study. *Wound Med.* 2014;4:1-4. PMID
10. Zelen CM, Serena TE, Snyder RJ. A prospective, randomised comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. *Int Wound J.* Apr 2014;11(2):122-128. PMID 24618401
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):724-732. 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):272-282. PMID 26695998
13. Kirsner RS, Sabolinski ML, Parsons NB, et al. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen.* Sep 2015;23(5):737-744. PMID 26100572
14. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix((R)) 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):554-560. PMID 25048468
15. 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 and Regeneration.* Nov-Dec 2014;22(6):688-693. PMID 25224019
16. Serena TE, Yaakov R, DiMarco D, et al. Dehydrated human amnion/chorion membrane treatment of venous leg ulcers: correlation between 4-week and 24-week outcomes. *J Wound Care.* Nov 2015;24(11):530-534. PMID 26551645
17. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix(R)) allograft for the treatment of venous leg ulcers. *Int Wound J.* Oct 11 2017. PMID 29024419
18. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved amniotic suspension for the treatment of knee osteoarthritis. *J Knee Surg.* Aug 2016;29(6):443-450. PMID 26683979
19. 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
20. Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. *Foot Ankle Int.* Feb 2015;36(2):151-158. PMID 25249320
21. 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):1332-1339. PMID 23945520
22. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea.* Aug 2005;24(6):654-660. PMID 16015082
23. 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):201-208. PMID 23062647
24. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev.* Feb 11 2016;2:CD011349. PMID 26867004
25. 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):484-491. PMID 26686968
26. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. *Ocul Surf.* Jul 2004;2(3):201-211. PMID 17216092

27. Clare G, Suleman H, Bunce C, et al. Amniotic membrane transplantation for acute ocular burns. *Cochrane Database Syst Rev.* Sep 12 2012;9(9):CD009379. PMID 22972141
28. Paris Fdos S, Goncalves 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):980-984. PMID 23723410
29. John T, Tighe S, Sheha H, et al. Corneal nerve regeneration after self-retained cryopreserved amniotic membrane in dry eye disease. *J Ophthalmol.* Aug 15 2017;2017:6404918. PMID 28894606
30. Cheng AM, Zhao D, Chen R, et al. Accelerated restoration of ocular surface health in dry eye disease by self-retained cryopreserved amniotic membrane. *Ocul Surf.* Jan 2016;14(1):56-63. PMID 26387870
31. Vlasov A, Sia RK, Ryan DS, et al. Sutureless cryopreserved amniotic membrane graft and wound healing after photorefractive keratectomy. *J Cataract Refract Surg.* Mar 2016;42(3):435-443. PMID 27063525