MASSACHUSETTS

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Medical Policy

Amniotic Membrane and Amniotic Fluid

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Policy Number: 643

BCBSA Reference Number: 7.01.149
NCD/LCD: N/A

Related Policies

- 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®, EpiCord®, Epifix®, Grafix™) may be considered **MEDICALLY NECESSARY**.

*Nonhealing 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.

Human amniotic membrane grafts with or without suture (eg, 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. Conservative therapy for neurotrophic keratitis may include 5 days of pressure patching, therapeutic contact lens, topical lubricants, and topical antibiotics.
- Corneal ulcers and melts that do not respond to initial conservative therapy. Conservative therapy for corneal ulcers and melts may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents.
- 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 to conservative therapy. A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment of a persistent epithelial defect may include 5 days of the following: topical lubricants, topical antibiotics, therapeutic contact lens, or patching.
- 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*** 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 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.

**** 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

***** Tear Film and Ocular Surface Society staged management for dry eye disease**

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)

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
Q4187	Epicord, per sq cm

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
H04.121	Dry eye syndrome of right lacrimal gland
H04.122	Dry eye syndrome of left lacrimal gland
H04.123	Dry eye syndrome of bilateral lacrimal glands
H04.129	Dry eye syndrome of unspecified lacrimal gland

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
H18.10	Bullous keratopathy, unspecified eye
H18.12	Bullous keratopathy, left eye
H18.13	Bullous keratopathy, bilateral
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
T26.50XA	Corrosion of unspecified eyelid and periocular area, initial encounter
T26.50XD	Corrosion of unspecified eyelid and periocular area, subsequent encounter
T26.50XS	Corrosion of unspecified eyelid and periocular area, sequela
T26.51XA	Corrosion of right eyelid and periocular area, initial encounter
T26.51XD	Corrosion of right eyelid and periocular area, subsequent encounter
T26.51XS	Corrosion of right eyelid and periocular area, sequela
T26.52XA	Corrosion of left eyelid and periocular area, initial encounter
T26.52XD	Corrosion of left eyelid and periocular area, subsequent encounter
T26.52XS	Corrosion of left eyelid and periocular area, sequela
T26.60XA	Corrosion of cornea and conjunctival sac, unspecified eye, initial encounter
T26.60XD	Corrosion of cornea and conjunctival sac, unspecified eye, subsequent encounter
T26.60XA	Corrosion of cornea and conjunctival sac, unspecified eye, sequela
T26.61XA	Corrosion of cornea and conjunctival sac, right eye, initial encounter
T26.61XD	Corrosion of cornea and conjunctival sac, right eye, subsequent encounter
T26.61XS	Corrosion of cornea and conjunctival sac, right eye, sequela
T26.62XA	Corrosion of cornea and conjunctival sac, left eye, initial encounter
T26.62XD	Corrosion of cornea and conjunctival sac, left eye, subsequent encounter
T26.62XS	Corrosion of cornea and conjunctival sac, left eye, sequela
T26.70XA	Corrosion with resulting rupture and destruction of unspecified eyeball, initial encounter
T26.70XD	Corrosion with resulting rupture and destruction of unspecified eyeball, subsequent encounter
T26.70XS	Corrosion with resulting rupture and destruction of unspecified eyeball, sequela
T26.71XA	Corrosion with resulting rupture and destruction of right eyeball, initial encounter
T26.71XD	Corrosion with resulting rupture and destruction of right eyeball, subsequent encounter
T26.71XS	Corrosion with resulting rupture and destruction of right eyeball, sequela
T26.72XA	Corrosion with resulting rupture and destruction of left eyeball, initial encounter
T26.72XD	Corrosion with resulting rupture and destruction of left eyeball, subsequent encounter
T26.72XS	Corrosion with resulting rupture and destruction of left eyeball, sequela
T26.80XA	Corrosions of other specified parts of unspecified eye and adnexa, initial encounter
T26.80XD	Corrosions of other specified parts of unspecified eye and adnexa, subsequent encounter
T26.80XS	Corrosions of other specified parts of unspecified eye and adnexa, sequela
T26.81XA	Corrosions of other specified parts of right eye and adnexa, initial encounter
T26.81XD	Corrosions of other specified parts of right eye and adnexa, subsequent encounter
T26.81XS	Corrosions of other specified parts of right eye and adnexa, sequela

T26.82XA	Corrosions of other specified parts of left eye and adnexa, initial encounter
T26.82XD	Corrosions of other specified parts of left eye and adnexa, subsequent encounter
T26.82XS	Corrosions of other specified parts of left eye and adnexa, sequela
T26.90XA	Corrosion of unspecified eye and adnexa, part unspecified, initial encounter
T26.90XD	Corrosion of unspecified eye and adnexa, part unspecified, subsequent encounter
T26.90XS	Corrosion of unspecified eye and adnexa, part unspecified, sequela
T26.91XA	Corrosion of right eye and adnexa, part unspecified, initial encounter
T26.91XD	Corrosion of right eye and adnexa, part unspecified, subsequent encounter
T26.91XS	Corrosion of right eye and adnexa, part unspecified, sequela
T26.92XA	Corrosion of left eye and adnexa, part unspecified, initial encounter
T26.92XD	Corrosion of left eye and adnexa, part unspecified, subsequent encounter
T26.92XS	Corrosion of left eye and adnexa, part unspecified, sequela

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
65778	Placement of amniotic membrane on the ocular surface; without sutures

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
H04.121	Dry eye syndrome of right lacrimal gland
H04.122	Dry eye syndrome of left lacrimal gland
H04.123	Dry eye syndrome of bilateral lacrimal glands
H04.129	Dry eye syndrome of unspecified lacrimal gland
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
H16.231	Neurotrophic keratoconjunctivitis, right eye
H16.232	Neurotrophic keratoconjunctivitis, left eye
H16.233	Neurotrophic keratoconjunctivitis, bilateral
H16.239	Neurotrophic keratoconjunctivitis, unspecified eye
H18.10	Bullous keratopathy, unspecified eye
H18.12	Bullous keratopathy, left eye
H18.13	Bullous keratopathy, bilateral
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
T26.50XA	Corrosion of unspecified eyelid and periocular area, initial encounter
T26.50XD	Corrosion of unspecified eyelid and periocular area, subsequent encounter
T26.50XS	Corrosion of unspecified eyelid and periocular area, sequela
T26.51XA	Corrosion of right eyelid and periocular area, initial encounter
T26.51XD	Corrosion of right eyelid and periocular area, subsequent encounter
T26.51XS	Corrosion of right eyelid and periocular area, sequela
T26.52XA	Corrosion of left eyelid and periocular area, initial encounter
T26.52XD	Corrosion of left eyelid and periocular area, subsequent encounter
T26.52XS	Corrosion of left eyelid and periocular area, sequela
T26.60XA	Corrosion of cornea and conjunctival sac, unspecified eye, initial encounter
T26.60XD	Corrosion of cornea and conjunctival sac, unspecified eye, subsequent encounter
T26.60XA	Corrosion of cornea and conjunctival sac, unspecified eye, sequela
T26.61XA	Corrosion of cornea and conjunctival sac, right eye, initial encounter
T26.61XD	Corrosion of cornea and conjunctival sac, right eye, subsequent encounter
T26.61XS	Corrosion of cornea and conjunctival sac, right eye, sequela
T26.62XA	Corrosion of cornea and conjunctival sac, left eye, initial encounter
T26.62XD	Corrosion of cornea and conjunctival sac, left eye, subsequent encounter
T26.62XS	Corrosion of cornea and conjunctival sac, left eye, sequela
T26.70XA	Corrosion with resulting rupture and destruction of unspecified eyeball, initial encounter
T26.70XD	Corrosion with resulting rupture and destruction of unspecified eyeball, subsequent encounter
T26.70XS	Corrosion with resulting rupture and destruction of unspecified eyeball, sequela
T26.71XA	Corrosion with resulting rupture and destruction of right eyeball, initial encounter
T26.71XD	Corrosion with resulting rupture and destruction of right eyeball, subsequent encounter
T26.71XS	Corrosion with resulting rupture and destruction of right eyeball, sequela
T26.72XA	Corrosion with resulting rupture and destruction of left eyeball, initial encounter
T26.72XD	Corrosion with resulting rupture and destruction of left eyeball, subsequent encounter
T26.72XS	Corrosion with resulting rupture and destruction of left eyeball, sequela
T26.80XA	Corrosions of other specified parts of unspecified eye and adnexa, initial encounter
T26.80XD	Corrosions of other specified parts of unspecified eye and adnexa, subsequent encounter
T26.80XS	Corrosions of other specified parts of unspecified eye and adnexa, sequela
T26.81XA	Corrosions of other specified parts of right eye and adnexa, initial encounter

T26.81XD	Corrosions of other specified parts of right eye and adnexa, subsequent encounter
T26.81XS	Corrosions of other specified parts of right eye and adnexa, sequela
T26.82XA	Corrosions of other specified parts of left eye and adnexa, initial encounter
T26.82XD	Corrosions of other specified parts of left eye and adnexa, subsequent encounter
T26.82XS	Corrosions of other specified parts of left eye and adnexa, sequela
T26.90XA	Corrosion of unspecified eye and adnexa, part unspecified, initial encounter
T26.90XD	Corrosion of unspecified eye and adnexa, part unspecified, subsequent encounter
T26.90XS	Corrosion of unspecified eye and adnexa, part unspecified, sequela
T26.91XA	Corrosion of right eye and adnexa, part unspecified, initial encounter
T26.91XD	Corrosion of right eye and adnexa, part unspecified, subsequent encounter
T26.91XS	Corrosion of right eye and adnexa, part unspecified, sequela
T26.92XA	Corrosion of left eye and adnexa, part unspecified, initial encounter
T26.92XD	Corrosion of left eye and adnexa, part unspecified, subsequent encounter
T26.92XS	Corrosion of left eye and adnexa, part unspecified, sequela

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

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 or cellesta duo, per square centimeter

Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
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
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid GF, 1 cc
Q4208	Novafix, per square centimeter
Q4209	Surgraft, per square centimeter
Q4210	Axolotl graft or axolotl dualgraft, per square centimeter
Q4211	Amnion bio or Axobiomembrane, per square centimeter
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter
Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
Q4218	Surgicord, per square centimeter
Q4219	Surgigraft-dual, per square centimeter
Q4221	Amniowrap2, per square centimeter
Q4227	Amniocore, per square centimeter
Q4228	BioNextPATCH, per square centimeter
Q4229	Cogenex amniotic membrane, per square centimeter.
Q4230	Cogenex flowable amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per square centimeter
Q4233	Surfactor or Nudyn, per 0.5 cc."
Q4234	Xcellerate, per square centimeter
Q4235	Amniorepair or altiply, per square centimeter
Q4236	carePATCH, per square centimeter
Q4237	Cryo-cord, per square centimeter
Q4238	Derm-maxx, per square centimeter
Q4239	Amnio-maxx or Amnio-maxx lite, per square centimeter
Q4240	Corecyte, for topical use only, per 0.5 cc
Q4241	Polycyte, for topical use only, per 0.5 cc
Q4242	Amniocyte plus, per 0.5 cc
Q4244	Procenta, per 200 mg
Q4245	Amniotext, per cc
Q4246	Coretext or Protext, per cc
Q4247	Amniotext patch, per square centimeter
Q4248	Dermacyte Amniotic Membrane Allograft, per square centimeter
Q4249	Amniply, for topical use only, per square centimeter
Q4250	Amnioamp-mp, per square centimeter
Q4254	Novafix dl, per square centimeter

Q4255	Reguard, for topical use only, 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.

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.

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 non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, 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, 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 2 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. 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. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for venous insufficiency ulcers. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy for this indication. 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

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. Relevant outcome 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. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 (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 outcome 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. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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 (SJS) who receive HAM, the evidence includes an RCT. Relevant outcome are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of SJS includes 1 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 SJS. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. 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. 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 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. 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. 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. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, 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 History

Date	Action
10/2020	Clarified coding information
7/2020	Clarified coding information
4/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2020	Clarified coding information.
10/2019	Clarified coding information.
7/2019	BCBSA National medical policy review. New medically necessary and investigational indications described. EpiCord added to medically necessary statement for diabetic lower extremity ulcers. Clarified coding information. Effective 7/1/2019.
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

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