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Subject: Amniotic Membrane and Limbal Stem Cell Transplantation for the Treatment of Ocular Conditions

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions	Related Guidelines
Other	References	Updates			

DESCRIPTION:

The cornea is the clear front of the eye and its surface is composed of an epithelium, a thin layer of stratified squamous cells that form the outermost layer of the cornea. The corneal epithelium can rapidly regenerate. This regeneration relies on the existence of stem cells located in the limbal epithelium (the junction zone between the corneal and conjunctival epithelia).

Amniotic membrane is the innermost layer of the placenta consisting of a thick basement membrane and an avascular stromal matrix. It can be obtained from cesarean deliveries and is prepared and cryo-preserved under sterile conditions. It may be sutured into place, or placed without sutures onto the ocular surface and used as a graft and/or a dressing to facilitate ocular surface reconstruction and promote healing. Amniotic membrane contains an avascular matrix, which inhibits angiogenesis in adjacent tissues, thus minimizing vascularization during ocular healing. It exhibits anti-inflammatory properties and suppresses expression of transforming growth factor-beta (TGF-β) isoforms, minimizing scar tissue.

Limbal stem cells act as a “barrier” to conjunctival epithelial cells and normally prevent them from migrating on to the corneal surface. Limbal stem cell deficiency (LSCD) can develop in traumatic, immunologic, or genetic diseases that affect the ocular surface. LSCD leads to conjunctivalization, with corneal vascularization and opacification and subsequent loss of vision. Limbal stem cell transplantation is a surgical treatment to address LSCD and restore a corneal epithelial phenotype. Based on the source of cells, limbal transplant can be autologous or allogenic. An autograft from the individual’s undamaged eye may be used, or an allograft from a donor’s eye may be used.

The goal of amniotic membrane transplantation and limbal stem cell transplantation is to reconstruct damaged ocular surfaces and promote healing, decrease scarring, reduce inflammation and restore function and appearance of corneal, conjunctival and eyelid tissues after injury due to trauma, disease, or surgery.

Summary and Analysis of Evidence: Human amniotic membrane grafts with or without suture and limbal stem cell transplantation have been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. Corneal ulcers and melts are uncommon and variable, and additional RCTs are not expected. No evidence was identified for corneal perforation when there is active inflammation after corneal transplant, and adjunctive treatment is required. Khokhar et al (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens. At the 3-month follow-up, 73% of patients in the HAM group showed complete epithelialization compared with 67% of patients in the conventional group. Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. The mean duration of treatment prior to ProKera insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome. Liu et al (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers. All but 1 of the studies was conducted outside of the U.S. There was 1 RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53%). Yin et al (2020) compared epithelialization and visual outcomes of 24 patients with corneal infectious ulcers and visual acuity of less than 20/200 who were treated with (n=11) or without (n=13) self-retained amniotic membrane. Utilization of amniotic membrane was initiated in their institution in 2018, allowing a retrospective comparison of the 2 treatment groups. Complete epithelialization occurred more rapidly and was reached in significantly more patients. Suri et al (2013) also reported on a series of 35 eyes of 33 patients who were treated with the self-retained ProKera HAM for a variety of ocular surface disorders. Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in 2 of 9 (22%) patients with this indication. Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency. Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional ProKera patch was used in 7 patients. An improvement in visual acuity was observed in all but 2 patients. Pachigolla et al (2009) reported a series of 20 patients who received a ProKera implant for ocular surface disorders; 6 of the patients had limbal stem cell deficiency with a history of chemical burn. Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40. The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception. dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy. Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve. Sharma et al (2016) conducted an RCT which assigned 25 patients (50

eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone. The application of c-HAM in the early stages of SJS resulted in improved visual acuity, better tear breakup time, improved Schirmer test results, and less conjunctival congestion. In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 44% of cases with corneal haze, 24% of cases of corneal vascularization and conjunctivalization, and 24% of cases of trichiasis and metaplastic lashes. Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease. They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis. John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment. The c-HAM was applied for an average of 3.4 days, while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both 1-month and 3-month follow-ups in the c-HAM group but not in the conventional treatment group. The treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM. A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months. An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011). Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but 8 of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the 2 groups for final visual outcome, symblepharon formation, corneal clarity or vascularization. A second RCT that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al (2019). Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 2 groups (2.06 logMAR for both groups). There was a trend for a decrease in corneal neovascularization; the study was not powered for this outcome. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified 4 RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence.

POSITION STATEMENT:

Human amniotic membrane grafts with or without suture **OR** limbal stem cell transplantation **meets the definition of medical necessity** for the treatment of any of the following ophthalmic conditions:

- 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 individuals 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
- Moderate or severe acute ocular chemical burn
- 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:

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:

- 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:

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

****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

Human amniotic membrane grafts with suture or glue also **meet the definition of medical necessity** 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 and limbal stem cell transplantation are considered **experimental or investigational** for all other ocular conditions, as there is a lack of clinical scientific evidence published in peer-reviewed literature to permit conclusions on safety and net health outcomes.

Injection of human amniotic fluid for the treatment of ophthalmic conditions is considered **experimental or investigational**. There is insufficient published clinical evidence to support safety and effectiveness.

BILLING/CODING INFORMATION:

CPT Coding:

65778	Placement of amniotic membrane on the ocular surface; without sutures
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
65780	Ocular surface reconstruction; amniotic membrane transplantation, multiple layers
65781	Ocular surface reconstruction; limbal stem cell allograft (eg, cadaveric or living donor)
65782	Ocular surface reconstruction; limbal conjunctival autograft (includes obtaining graft)

HCPCS Coding:

V2790	Amniotic membrane for surgical reconstruction, per procedure

ICD-10 Diagnosis Codes That Support Medical Necessity:

H04.121 – H04.129	Dry eye syndrome
H11.001 – H11.069	Pterygium
H11.151 – H11.153	Pinguecula
H11.21 – H11.213	Conjunctival scars
H11.221 – H11.223	Conjunctival adhesions and strands (localized)
H11.231 – H11.233	Conjunctival granuloma
H11.241 – H11.243	Symblepharon
H11.31 – H11.33	Conjunctival hemorrhage
H11.411 – H11.413	Vascular abnormalities of conjunctiva
H11.441 – H11.443	Conjunctival cysts
H11.811 – H11.819	Pseudopterygium
H16.001 – H16.049	Corneal ulcer
H16.051 – H16.053	Superficial keratitis
H16.061 – H16.079	Mycotic and perforated corneal ulcer
H16.111 – H16.113	Macular keratitis
H16.121 – H16.123	Filamentary keratitis
H16.131 – H16.133	Photokeratitis
H16.141 – H16.143	Punctate keratitis
H16.231 – H16.239	Neurotrophic keratoconjunctivitis
H16.241 – H16.243	Ophthalmia nodosa
H16.251 – H16.253	Phlyctenular keratoconjunctivitis
H16.261 – H16.263	Vernal keratoconjunctivitis, with limbar and corneal involvement
H16.311 – H16.313	Corneal abscess
H16.321 – H16.323	Diffuse interstitial keratitis
H16.331 – H16.333	Sclerosing keratitis
H16.391 – H16.393	Other interstitial and deep keratitis

H16.421 – H16.423	Pannus (corneal)
H16.431 – H16.433	Localized vascularization of cornea
H16.441 – H16.443	Deep vascularization of cornea
H17.00 – H17.03	Adherent leukoma
H17.10 – H17.12	Central corneal opacity
H17.811 – H17.813	Minor opacity of cornea
H17.821 – H17.823	Peripheral opacity of cornea
H18.021 – H18.023	Argentous corneal deposits
H18.031 – H18.033	Corneal deposits in metabolic disorders
H18.041 – H18.043	Kayser-Fleischer ring
H18.10 – H18.13	Bullous keratopathy
H18.311 – H18.313	Idiopathic corneal edema
H18.321 – H18.323	Folds in Descemet's membrane
H18.331 – H18.333	Rupture in Descemet's membrane
H18.411 – H18.413	Arcus senilis
H18.43	Other calcerous corneal degeneration
H18.441 – H18.443	Keratomalacia
H18.451 – H18.453	Nodular corneal degeneration
H18.461 – H18.463	Peripheral corneal degeneration
H18.50 – H18.59	Corneal dystrophy
H18.711 – H18.713	Corneal ectasia
H18.721 – H18.723	Corneal staphyloma
H18.731 – H18.733	Descemetocele
H18.811 – H18.813	Anesthesia and hypoesthesia of cornea
H18.821 – H18.839	Erosion of cornea
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L51.0 – L51.9	Erythema multiforme [Stevens-Johnson syndrome]
T26.11XD,S – T26.12D,S	Burn of cornea and conjunctival sac
T26.21D,S – T26.22D,S	Burn with resulting rupture and destruction of eyeball
T26.31D,S – T26.32,D,S	Burns of other specified parts of eye and adnexa
T26.41D,S – T2642D,S	Burn of eye and adnexa
T26.61D,S – T26.62D,S	Corrosion of cornea and conjunctival sac
T26.71D,S – T26.72D,S	Corrosion with resulting rupture and destruction of eyeball
T26.81D,S – T26.82D,S	Corrosions of other specified parts of eye and adnexa

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Bullous keratopathy: the presence of corneal epithelial bullae, resulting from corneal endothelial disease (failure of the corneal endothelium to maintain the normally dehydrated state of the cornea).

Hereditary aniridia: a congenital, hereditary, bilateral, extreme form of iris hypoplasia in which the iris appears absent on superficial clinical examination.

Neurotrophic keratopathy: a degenerative disease of the corneal epithelium resulting from impaired corneal innervation. Symptoms include reduction in corneal sensitivity or complete corneal anesthesia. This disease is responsible for producing epithelial keratopathy, ulceration and perforation.

Pseudopterygium: a conjunctival scar joined to the cornea; it looks like a pterygium but is not attached to the tissue.

Pterygium: a fleshy triangular growth of bulbar conjunctiva that may spread across and distort the cornea, induce astigmatism, and change the refractive power of the eye.

Stevens-Johnson syndrome: a severe cutaneous hypersensitivity reaction; drugs, especially sulfa drugs, antiepileptics, and antibiotics, are the most common causes. Macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing.

RELATED GUIDELINES:

None applicable.

OTHER:

Other names and terms used to report amniotic membrane and amniotic fluid preparations:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Prokera®

AmbioDisk™

AmnioGraft®

Artacent® Ocular

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 06/27/24.

GUIDELINE UPDATE INFORMATION:

02/15/15	New Medical Coverage Guideline.
10/01/15	Revision; updated ICD9 and ICD10 coding sections.
02/15/16	Scheduled review. Maintained position statement. Revised program exceptions section and updated references.
03/15/17	Scheduled review. Maintained position statement. Updated references. Reformatted guideline.
03/15/18	Scheduled review. Maintained position statement; updated references.
04/15/19	Scheduled review. Revised position statement and ICD10 coding section. Updated references.
04/15/20	Scheduled review. Revised description, position statement, and index terms. Updated references.
06/15/21	Scheduled review. Maintained position statement and updated references.
07/15/23	Scheduled review. Maintained position statement and updated references.
08/21/23	Update to Program Exceptions section.
07/15/24	Scheduled review. Revised description and maintained position statement. Updated references.