Name of Policy:
Amniotic Membrane Transplantation for the Ocular Surface

Policy #: 624  Latest Review Date: July 2017
Category: Medical  Policy Grade: C

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
The outermost layer of the cornea, the clear layer of the eye, has a surface that is composed of an epithelium, a thin layer of stratified squamous cells. The corneal epithelium has the ability to rapidly regenerate and this regeneration relies on stem cells located in the limbal epithelium (the junction zone between the corneal and conjunctival epithelia).

Corneal epithelial defects are a focal loss of the corneal epithelium. Persistent corneal epithelial defects refractory to conventional treatment remain a therapeutic challenge, often requiring surgical intervention. Symptoms associated with these defects can include pain, photophobia, tearing and a sensation of a foreign body in the eye. Corneal defects can be caused by:

- Corneal dryness and systemic disorders leading to corneal dryness (e.g., Sjogren’s syndrome, Vitamin A deficiency, dry eye syndrome and thyroid eye disease)
- Deficiency of the limbal cells or failure to regenerate epithelial cells
- Ultraviolet burns (e.g., prolonged sun exposure off reflective surfaces, welding)
- Exposure of eye (e.g., neurotrophic diseases causing incomplete eyelid closure, proptosis, restrictive eyelid diseases)
- Mechanical trauma of the cornea (e.g., chemical exposure, foreign body in the lid/fornices/trichiasis/distichiasis, contact lens overuse, fingernail scratch)

Amniotic membrane transplantation (AMT) has been proposed as a treatment of ocular conditions. AMT is also being investigated for use in the restructuring of damaged ocular surfaces and as an aid in the healing of damaged ocular tissues. Ocular injuries due to trauma or disease damage the cornea and limbal epithelium. The corneal surface cannot regenerate if the damage to the epithelium is extensive. This results in ulcerations and loss of tissue to the extent of stem cell deficiency. This ulceration often fails to heal normally and can lead to vision loss. Amniotic membrane-covered surfaces are reported to induce rapid re-epithelialization in as little as 2 to 4 weeks, resulting in a smooth, wettable surface, with reduced inflammation, vascularization and scarring. This, in turn, allows for successful surface reconstruction.

**Human Amniotic Membrane**
Human amniotic membrane (HAM) consists of two conjoined layers, the amnion and chorion, and forms the innermost lining of the 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.

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. There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause substantial immune response. It is believed that these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one dehydrated HAM product has been shown to elute growth
factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.

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.

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.

Policy:
Effective for dates of service on or after May 6, 2016:
Amniotic membrane transplantation for the treatment of corneal conditions refractory to conventional treatment using grafts that are fixated using sutures, glue fixation, secured under a bandage contact lens, self-contained or unfixated (e.g., Prokera®) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for any the following conditions:

- Absence of iris;
- Bullous keratopathy;
- Conjunctivochalasis;
- Corneal degeneration;
- Corneal ectasia, corneal staphyloma, descemetocele or other corneal deformity;
- Corneal ulceration or defect;
- Corneal disorder due to contact lens or recurrent erosion of cornea;
- Following removal of conjunctival lesion(s);
- Hereditary corneal dystrophies;
- Neurotrophic keratoconjunctivitis;
- Ocular burns;
- Stevens-Johnson Syndrome;
- Pterygium;
- Pseudopterygium

Amniotic membrane transplantation for the treatment of dry eye syndrome and any other conditions not listed above does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the
member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
The most recent literature update was performed through November 20, 2016.

Amniotic membrane obtained from cesarean deliveries is cryo-preserved and can be applied to the ocular surface, either sutured or unsutured. Studies support that amniotic membrane-covered surfaces often demonstrate rapid re-epithelialization and reduced inflammation and scarring which promotes successful ocular surface reconstruction. Most of the available studies were with patients with symptomatic bullous keratopathy with intractable pain and poor visual potential. Many studies have been conducted outside the United States, were of very small sample size, and not randomized or controlled for the most part (due to the nature of the injuries and treatment).

**Sutured HAM Graft for ophthalmologic conditions**
Sutured HAM graft has been evaluated for a variety of ophthalmologic conditions.

**Neurotrophic Keratitis**
In 2005, Khokhar and Natung reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or to conventional treatment with tarsorrhaphy or bandage contact lens. At the three-month follow-up, 11 (73.3%) of 15 patients in the HAM group showed complete epithelialization compared to ten (66.7%) of 15 in the conventional group. This difference was not significantly significant.

**Following Pterygium Repair**
A number of RCTs have been reported on use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified four 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.

**Stevens-Johnson Syndrome**
One RCT from India (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or to medical therapy alone. The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of Stevens-Johnson syndrome resulted in improved visual acuity (p=0.042), tear breakup time (p=0.015), Schirmer test results (p<0.001), and less conjunctival congestion (p=0.03). 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 compared dramatically with the medical therapy alone group, which had 11 (44%) of 25 cases with corneal haze (p=0.001), 6 (24%) cases of corneal...
vascularization and conjunctivalization (p=0.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

Persistent Epithelial Defects and Ulceration
In 2004, Bouchard and John wrote a review 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 rarity of the diseases and the absence of a 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.

Ocular Burns
A 2012 Cochrane review evaluated the evidence on HAM graft for acute ocular burns. Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to c-HAM plus medical therapy or to medical therapy alone. In the subset of 36 patients with moderate ocular burns treated within seven days, 13 (65.0%) of 20 control eyes and 14 (87.5%) of 16 AMT-treated eyes had complete epithelialization by 21 days. There was a trend (p=0.09) toward a reduced relative risk of failure of epithelization in the treatment group. Mean logarithm of the minimum angle of resolution (logMAR) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within seven days, one (5.9%) of 17 AMT-treated eyes and one (6.7%) of 15 control eyes were epithelialized by day 21. There was no significant difference in final visual acuity, which was 1.77 logMAR in the treated eyes and 1.64 in the control group (p=NS). The risk of bias was considered high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. Reviewers determined that conclusive evidence supporting the treatment of acute ocular surface burns with AMT is lacking.

Bullous Keratopathy
Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation. In 2013, Dos Santos Paris et al published an RCT that compared fresh HAM to 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 two treatments. Symptoms had been present for approximately two 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 pain did not resolve.

Dry Eye Syndrome, Corneal Perforation, and Limbus Stem Cell Deficiency
No RCTs were identified on these other ophthalmic indications.
Section Summary: Sutured HAM Graft for Ophthalmic Conditions
The most widely studied condition with a technology assessment evaluating RCT evidence is use of HAM following pterygium repair. The assessment concluded, based on four RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT on HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to those for conventional therapy. One RCT has shown that application of c-HAM in the early stages of Stevens-Johnson syndrome leads to clinically significant improvement compared to medical therapy alone. A 2012 Cochrane review found one RCT evaluating HAM graft for acute ocular burns. The trial suggested a benefit for HAM in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and lack of masking to treatment condition. A trial on HAM for the treatment of bullous keratopathy reported that there was no difference in clinical outcomes between HAM and stromal puncture. Other indications have been studied only in case series.

HAM Without Suture for Ophthalmic Conditions
Traditionally, amniotic membrane has been fixed onto the eye with sutures or glue or placed under a bandage contact lens for a variety of ocular surface disorders. Several devices have been reported that use a ring around a c-HAM allograft that allows it to be inserted under topical anesthesia similar to insertion of a contact lens. The easier insertion may lead to more widespread use, such as dry eye disease and for healing after photorefractive keratectomy (PRK).

Dry Eye Disease
The Prokera c-HAM device was evaluated in a 2016 series by Cheng et al. The senior author of the study (S.C.G. Tseng) holds the patent on Prokera. This retrospective review assessed ten patients treated with the self-retained device for moderate-to-severe dry eye disease. In this study, these ten patients had moderate-to-severe dry eye syndrome despite conventional medical treatment. The c-HAM device was placed in 15 eyes (one eye at a time) for a mean of 4.9 days (range, 2-8 days), after which the c-HAM was either dissolved or cloudy. Treatment resulted in symptomatic relief for a mean of 4.2 months (range, 0.3 to 6.8 months) after a single treatment. Symptomatic improvement was accompanied by statistically significant reductions of Ocular Surface Disease Index scores, use of topical medications, conjunctival hyperemia, corneal staining (all p<0.001), and a trend toward improved visual acuity (p=0.06).

Photorefractive Keratectomy
In 2016, Vlasov et al reported on a prospective, nonrandomized controlled trial evaluating the effect of sutureless amniotic membrane (Prokera) on corneal wound healing after PRK. Forty patients (80 eyes) had PRK for myopia. After surgery, a high-oxygen-transmissible bandage contact lens was applied on the dominant eye and cryopreserved amniotic membrane on the nondominant eye. Patients were assessed daily until complete corneal re-epithelialization occurred in both eyes and then at two weeks and 1, 3, 6, and 12 months thereafter. The primary outcome was re-epithelialization, which was assessed daily with slitlamp examination, fluorescein staining, and photography. The time to complete reepithelialization was faster in eyes treated with a bandage contact lens (3.7 days; range, 3-7 days) than with the amniotic membrane product (4.6 days; range, 3-16 days). Initially, patients reported greater discomfort and dryness with amniotic membrane. Visual and clarity and optical quality of the cornea were similar between the amniotic membrane graft eyes and bandage contact lens eyes.
Other
Use of Prokera has also been reported for refractory 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 (referenced in Cheng et al, 2016).

**Section Summary: HAM Without Suture for Ophthalmic Conditions**
Current evidence on use of the Prokera device includes one within-subject comparative study and case series. While the case series reported generally positive effects, RCTs are needed to determine the effect of sutureless self-contained HAM on corneal healing. The single prospective comparative trial identified found no benefit of HAM compared to a bandage contact lens when used for wound healing after PRK. RCTs are needed to determine whether HAM improves healing for these various disorders.

**Summary of Evidence**
**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 four 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 two RCTs and a systematic review that included one RCT. 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 other 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 one 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 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 use of the Prokera device is limited. While the case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs are needed to determine whether HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

A review of the literature has shown that amniotic membrane has been used for nearly two decades for ophthalmic disorders, although RCT evidence is limited. Therefore, clinical input was requested on the specific disorders for which amniotic membrane would be expected to improve health outcomes and use is consistent with generally accepted medical practice. Input supported the use of sutured or glued amniotic membrane for neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Those providing input at the time had lower confidence that sutureless amniotic membrane performed as well or better than sutured amniotic membrane.

**Clinical Input**

**Objective**

In 2017, clinical input was sought to help determine the appropriate use in clinical practice of human amniotic membrane (also referred to as amniotic membrane graft [AMG]) for ophthalmic disorders.

**Respondents**

Clinical input was provided on behalf of the American Academy of Ophthalmology (AAO) by Dr. David Glasser, Chair of AAO’s Health Policy Committee.

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by the specialty society is attributed to the individual physician and is not a statement from the specialty society. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a special society and/or physician member designated by the specialty society or clinical health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.
Additional Comments
With regard to the nine indications listed above, there was lower range confidence that there is adequate evidence demonstrating that sutureless fixation HAM (also called amniotic membrane graft [AMG]) (eg, Prokera, AmbioDisk) performs as well as or better than sutured or glued AMG.

Use of AMG would be expected to improve health outcomes and is considered consistent with generally accepted medical practice for:

- “patients with an epithelial defect that (1) has failed to completely close after five days of conservative treatment (2) has failed to demonstrate a decrease in size after two days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to AMG. AMG requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day.”
- “We are in agreement that larger controlled studies are needed to show benefit of AMG in dry eye disease, where the disease is common and such studies should be easy to perform.”
U.S. Preventive Services Task Force Recommendations
Not applicable.

**Key Words:**
Absence of iris; Amniotic membrane transplantation; AMT; dry eye syndrome; keratopathy; bullous keratopathy; conjunctivochalasis; corneal degeneration; corneal ectasia; corneal staphyloma; descemetocele; other corneal deformity; corneal ulceration; corneal defect; corneal disorder due to contact lens or recurrent erosion of cornea; conjunctival lesion removal; hereditary corneal dystrophies; neurotrophic keratoconjunctivitis; ocular burns; pterygium; pseudopterygium; Stevens-Johnsons Syndrome; SJS; Prokera

**Approved by Governing Bodies:**
Human amniotic membrane is considered to be minimally processed and not significantly changed in structure from the natural material; FDA classifies it as banked human tissue and therefore, it does not require FDA approval.

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Human amniotic membrane products and amniotic fluid products are included in these regulations.

In 2003, Prokera™ was cleared for marketing by FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). FDA determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera™ device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.”

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:

- **65778** Placement of amniotic membrane on the ocular surface; without sutures
- **65779** ; single layer, sutured
- **65780** Ocular surface reconstruction; amniotic membrane transplantation, multiple layers
References:


Policy History:
Medical Policy Administration Committee, March 2016
Available for comment March 4 through April 25, 2016 May 5, 2016
Medical Policy Group, May 2016 (3): Updated literature review and clarified/expanded policy statement indications; updated Key Words & References
Medical Policy Administration Committee, May 2016
Medical Policy Panel, May 2017
Medical Policy Group, July 2017 (3): 2017 Updates on Description, Key Points, Governing Bodies, Key Words & References; clarified policy statements with types of grafts approved to coincide with coding and moved regulatory language to Governing Bodies section – no change in intent

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.