

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

Effective Date:	1/1/2024
-----------------	----------

[POLICY
RATIONALE
DISCLAIMER
POLICY HISTORY](#)

[PRODUCT VARIATIONS
DEFINITIONS
CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND
BENEFIT VARIATIONS
REFERENCES](#)

I. POLICY

Treatment of non-healing diabetic lower-extremity ulcers using the following human amniotic membrane products: Affinity® (Q4159), AmnioBand® Membrane (Q4151, Q4168), Biovance® (Q4154), EpiCord® (Q4187), Epifix® (Q4186), Grafix® (Q4132, Q4133), Celera Dual Membrane™ (Q4259), Signature APatch (Q4260) may be considered **medically necessary**.

Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) (65778, 65779, 65780, Q4100, V2790) may be considered **medically necessary** for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy;
- Corneal ulcers and melts that do not respond to initial conservative therapy;
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
- Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., 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 (examples of conservative therapy include 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 (see Policy Guidelines); or
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue (65779, 65780, V2790) 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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

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, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures (A4100, Q4100, Q4139, Q4145, Q4155, Q4162, Q4171, Q4174, Q4177, Q4230, Q4233, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246).

Injection of human amniotic fluid is considered **investigational** for all indications as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) and indications not listed above are considered **investigational** including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure. (A4100, Q4100, Q4137, Q4138, Q4140, Q4148, Q4150, Q4153, Q4156, Q4157, Q4160, Q4163, Q4169, Q4170, Q4173, Q4176, Q4178, Q4180, Q4181, Q4183, Q4184, Q4185, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4199, Q4201, Q4204, Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4220, Q4221, Q4224, Q4225, Q4227, Q4229, Q4231, Q4232, Q4234, Q4235, Q4237, Q4239, Q4247, Q4248, Q4249, Q4250, Q4251, Q4252, Q4253, Q4254, Q4255, Q4256, Q4257, Q4258, Q4261, Q4263, Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271, Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283, Q4284, Q4285, Q4286)

POLICY GUIDELINES

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

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)

Step 1:

- Education regarding the condition, its management, treatment, and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

- 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 (e.g., tarsorrhaphy, salivary gland transplantation)

Dry eye severity level DEWS 3 to 4

Discomfort, severity, and frequency - Severe frequent or constant

Visual symptoms - chronic and/or constant, limiting to disabling

Conjunctival Injection - +/- or +/+

Conjunctive Staining - moderate to marked

Corneal Staining - marked central or severe punctate erosions

Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris

Lid/meibomian glands - Frequent

Tear film breakup time - < 5

Schirmer score (mm/5 min) - < 5

Cross-reference:

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

MP 2.033 Recombinant and Autologous Platelet Derived Growth Factors as Treatment of Wound Healing and Other Non-Orthopedic Conditions

MP 1.017 Bio-Engineered Skin and Soft Tissue Substitutes

MP 4.039 Orthopedic Applications of Platelet Rich Plasma

MP 2.028 Eye Care

MP 4.033 Diagnosis and Treatment of Dry Eye Syndrome

II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual MP-7.01.149 Amniotic Membrane and Amniotic Fluid Injections. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

[TOP](#)

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.

Human Amniotic Membrane (HAM)

HAM consists of two 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 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 these properties are retained in cryopreserved HAM and HAM products, resulting in a readily available tissue with regenerative potential. In support, one 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

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

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 evidence review MP 2.080.

Regulatory Status

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, Title 21, parts 1270 and 1271. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps),⁴

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

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

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4. Either:
 - i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
 - ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 - a. Is for autologous use;
 - b. Is for allogeneic use in a first-degree or second-degree blood relative; or
 - c. Is for reproductive use."

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

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

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

In 2003, Prokera™ was cleared for marketing by the Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The Food and Drug Administration determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera™ device is intended "for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred."⁵ The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

AmnioClip (FORTECH GmbH) is a ring designed to hold the 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.

IV. RATIONALE

[TOP](#)

SUMMARY OF EVIDENCE

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 (i.e., Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life (QOL). The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

(<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 (i.e., Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in 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 two RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of lower-extremity venous ulcers includes two multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at four weeks but the percentage of patients with complete wound closure did not differ between EpiFix and the standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. 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. The relevant outcomes are symptoms, functional outcomes, QOL, 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

Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

Neurotrophic Keratitis with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. 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, which does not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-randomized comparative study. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. The systematic review showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with twenty-two patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. No comparative evidence was identified for this indication. 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 (e.g., endothelial, or penetrating keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial, or penetrating keratoplasty) who receive HAM, the evidence includes RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

Partial Limbal Stem Cell Deficiency (LSCD) with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient

For individuals who have partial LSCD with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative trials were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. The evidence is insufficient to determine that the technology

Moderate or Severe Stevens-Johnson Syndrome

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of Stevens-Johnson includes one RCT with twenty-five patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Persistent Epithelial Defects and Ulceration That does not Respond to Conservative Therapy

For individuals who have persistent epithelial defects that does not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative trials were identified on persistent epithelial defects and ulceration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Severe Dry Eye with Ocular Surface Damage and Inflammation That does not Respond to Conservative Therapy

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with twenty patients and a retrospective series of eighty-four patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. 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

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation, however, HAM may provide temporary coverage of the severe defect when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Repair Following Mohs Micrographic Surgery

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

Definitions

N/A

[Top](#)

V. BENEFIT VARIATIONS

[Top](#)

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VI. DISCLAIMER

[TOP](#)

Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered skin substitutes:

See investigational section of policy above

Covered when medically necessary, for treatment of non-healing diabetic lower-extremity ulcers:

HCPCS Codes						
Q4132	Q4133	Q4151	Q4154	Q4159	Q4168	Q4186
Q4187	Q4259	Q4260	Q4262	Q4287	Q4288	Q4289
Q4290	Q4291	Q4292	Q4296	Q4297	Q4298	Q4299
Q4300	Q4301	Q4302	Q4303			

Current Procedural Terminology (CPT) copyrighted by American Medical Association. All Rights Reserved.

ICD-10-CM Diagnosis Codes	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

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

ICD-10-CM Diagnosis Codes	Description
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

Amniotic membrane grafts that are with or without sutures, with glue may be considered medically necessary, for the ophthalmic indications above:

Procedure Codes							
65778	65779	65780	Q4100	V2790			

ICD-10-CM Diagnosis Codes	Description
H11.001	Unspecified pterygium of right eye
H11.002	Unspecified pterygium of left eye
H11.003	Unspecified pterygium of eye, bilateral
H11.011	Amyloid pterygium of right eye
H11.012	Amyloid pterygium of left eye
H11.013	Amyloid pterygium of eye, bilateral
H11.021	Central pterygium of right eye
H11.022	Central pterygium of left eye
H11.023	Central pterygium of eye, bilateral
H11.031	Double pterygium of right eye
H11.032	Double pterygium of left eye
H11.033	Double pterygium of eye, bilateral
H11.041	Peripheral pterygium, stationary, right eye
H11.042	Peripheral pterygium, stationary, left eye
H11.043	Peripheral pterygium, stationary, bilateral
H11.051	Peripheral pterygium, progressive, right eye
H11.052	Peripheral pterygium, progressive, left eye
H11.053	Peripheral pterygium, progressive, bilateral
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

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

ICD-10-CM Diagnosis Codes	Description
H16.001	Unspecified corneal ulcer, right eye
H16.002	Unspecified corneal ulcer, left eye
H16.003	Unspecified corneal ulcer, bilateral
H16.011	Central corneal ulcer, right eye
H16.012	Central corneal ulcer, left eye
H16.013	Central corneal ulcer, bilateral
H16.021	Ring corneal ulcer, right eye
H16.022	Ring corneal ulcer, left eye
H16.023	Ring corneal ulcer, bilateral
H16.031	Corneal ulcer with hypopyon, right eye
H16.032	Corneal ulcer with hypopyon left eye
H16.033	Corneal ulcer with hypopyon, bilateral
H16.041	Marginal corneal ulcer, right eye
H16.042	Marginal corneal ulcer, left eye
H16.043	Marginal corneal ulcer, bilateral
H16.051	Mooren's corneal ulcer, right eye
H16.052	Mooren's corneal ulcer, left eye
H16.053	Mooren's corneal ulcer, bilateral
H16.061	Mycotic corneal ulcer, right eye
H16.062	Mycotic corneal ulcer, left eye
H16.063	Mycotic corneal ulcer, bilateral
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
H18.11	Bullous keratopathy, right 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, eft eye
H18.833	Recurrent erosion of cornea, bilateral
H18.839	Recurrent erosion of cornea, unspecified eye
H18.891	Other specified disorders of cornea, right eye
H18.892	Other specified disorders of cornea, left eye

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

ICD-10-CM Diagnosis Codes	Description
H18.893	Other specified disorders of cornea, bilateral
L51.1	Stevens-Johnson syndrome

VIII. REFERENCES

[TOP](#)

1. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane, and amniotic fluid-derived cells: potential tools for regenerative medicine? *Regen Med.* Mar 2009; 4(2): 275-91. PMID 19317646
2. Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. *Int Wound J.* Oct 2013; 10(5): 493-500. PMID 23902526
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. *J Bone Joint Surg.* 1938; 20(I):167-177.
4. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. 2017 Accessed March 17, 2022.
5. Food and Drug Administration. 510(k) Summary: ProKera™ Bio-Tissue Inc. (K032104). 2003; Accessed March 17, 2022.
6. Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. *J Comp Eff Res.* Jan 2020; 9(1): 23-34. PMID 31691579
7. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. *Wound Repair Regen.* May 2018; 26(3): 274-283. PMID 30098272
8. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. *Int Wound J.* Feb 2019; 16(1): 122-130. PMID 30246926
9. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. *Int Wound J.* Dec 2018; 15(6): 950-957. PMID 30019528
10. Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. *Wounds.* Mar 2016; 28(3): 70-7. PMID 26978860
11. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

- chronic lower extremity diabetic ulcers. Int Wound J. Dec 2015; 12(6): 724-32. PMID 25424146*
12. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int Wound J. Apr 2016; 13(2): 272-82. PMID 26695998*
 13. Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. *Int Wound J. Feb 2019; 16(1): 19-29. PMID 30136445*
 14. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix ((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J. Oct 2014; 11(5): 554-60. PMID 25048468*
 15. Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. *Wounds. Jun 2015; 27(6): 158-69. PMID 26061491*
 16. Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. *Int Wound J. Jun 2017; 14(3): 569-577. PMID 27489115*
 17. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. *Wound Repair Regen. Nov-Dec 2014; 22(6): 688-93. PMID 25224019*
 18. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix (R)) allograft for the treatment of venous leg ulcers. *Int Wound J. Feb 2018; 15(1): 114-122. PMID 29024419*
 19. Bianchi C, Tettelbach W, Istwan N, et al. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. *Int Wound J. Jun 2019; 16(3): 761-767. PMID 30864259*
 20. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. *J Knee Surg. Aug 2016; 29(6): 443-50. PMID 26683979*
 21. Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. *Br J Sports Med. Nov 2016; 50(22): 1367-1375. PMID 27143138*
 22. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. *Foot Ankle Int. Oct 2013; 34(10): 1332-9. PMID 23945520*
 23. Cazzell S, Stewart J, Agnew PS, et al. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

- Placebo for the Treatment of Plantar Fasciitis. Foot Ankle Int. Oct 2018; 39(10): 1151-1161. PMID 30058377*
24. Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. *Eye Contact Lens. Sep 2013; 39(5): 341-7. PMID 23945524*
 25. Liu J, Li L, Li X. Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis. *Cornea. Apr 2019; 38(4): 454-462. PMID 30702468*
 26. Yin HY, Cheng AMS, Tighe S, et al. Self-retained cryopreserved amniotic membrane for treating severe corneal ulcers: a comparative, retrospective control study. *Sci Rep. Oct 12, 2020; 10(1): 17008. PMID 33046729*
 27. Paris Fdos S, Goncalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. *Br J Ophthalmol. Aug 2013; 97(8): 980-4. PMID 23723410*
 28. Kheirkhah A, Casas V, Raju VK, et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. *Am J Ophthalmol. May 2008; 145(5): 787-94. PMID 18329626*
 29. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. *Eye Contact Lens. Jul 2009; 35(4): 172-5. PMID 19474753*
 30. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens - Johnson syndrome: A Randomized Control Trial. *Ophthalmology. Mar 2016; 123(3): 484-91. PMID 26686968*
 31. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. *Ocul Surf. Jul 2004; 2(3): 201-11. PMID 17216092*
 32. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. *J Ophthalmol. 2017; 2017: 6404918. PMID 28894606*
 33. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DREAM study. *Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328*
 34. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. *Br J Ophthalmol. Feb 2011; 95(2): 199-204. PMID 20675729*
 35. Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial. *Am J Ophthalmol. Mar 2019; 199: 209-215. PMID 30419194*
 36. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. *Ophthalmology. Nov 2005; 112(11): 1963-9. PMID 16198422*
 37. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. *Ophthalmology. Jan 2013; 120(1): 201-8. PMID 23062647*

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

38. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev.* Feb 11, 2016; 2: CD011349. PMID 26867004
39. Toman J, Michael GM, Wisco OJ, et al. Mohs Defect Repair with Dehydrated Human Amnion/Chorion Membrane. *Facial Plast Surg Aesthet Med.* Jan-Feb 2022; 24(1): 48-53. PMID 34714143
40. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg.* Feb 2016; 63(2 Suppl): 3S-21S. PMID 26804367
41. Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair Regen.* Jan-Feb 2016; 24(1): 112-26. PMID 26663430
42. Blue Cross Blue Shield Association Medical Policy Reference Manual. 7.01.149, Amniotic Membrane and Amniotic Fluid Injections. March 2022.

IX. POLICY HISTORY

[TOP](#)

MP-4.042	04/20/20 Consensus review. No changes to policy statements.
	05/29/20 Admin update. New codes added; effective 7/1/20
	10/01/20 Admin Update. New codes Q4249 and Q4255 added; effective 10/01/2020.
	4/20/21 Minor review. Added Affinity (Q4159) an MN when criteria are met. Deleted Q4202 and Q4222. Added as investigational: Q4217, Q4228, Q4248, Q4250, Q4254, Q4239, Q4235, Q4237, Q4241, Q4234
	9/22/21 Admin update. New codes added as experimental and investigational, Q4251, Q4252, Q4253; effective 10-1-21.
	12/2/21 Admin update. New code Q4199 added as experimental and investigational; effective 1-1-22.
	3/11/22 Admin update. New codes added: Q4224, Q4225, Q4256, Q4257, Q4258, as investigational; A4100 (NOS code) determination of coverage will be determines by criteria; effective 4-1-22.
	3/17/22 Consensus review. Removed table 1. Investigational coding removed from coding section will remain within the investigational section of the policy only. Removed end-dated code Q4228. Investigational statement expanded to include Mohs surgery; this is for clarification only - "all other indications" was already considered investigational. References updated.
	6/13/2022 Administrative Update. New codes Q4259 and Q4260 added as medically necessary. New code Q4261 added as investigational. Formatting updated. Effective 7/1/2022.
	7/21/22 Administrative update. Code V2790 corrected in table. Correct in criteria.
	11/29/22 Administrative update. Codes Q4262 & Q4263 added effective 1/1/23.
	3/16/23 Administrative update. New codes Q4265-Q4271 added effective 4/1/23.

MEDICAL POLICY

POLICY TITLE	AMNIOTIC MEMBRANE AND AMNIOTIC FLUID INJECTIONS
POLICY NUMBER	MP-4.042

	6/15/2023 Administrative update. New codes Q4284, Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283 added effective 7/1/23
	9/7/2023 Administrative update. New Codes Q4285 and Q4286 added effective 10/1/23.
	10/23/2023 Retirement. To be combined into new policy.
	12/13/2023 Added new codes Q4287-Q4290, Q4292, Q4295-Q4303 effective 1/1/2024.

[Top](#)

Health care benefit programs issued or administered by Capital Blue Cross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company®, and Keystone Health Plan® Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.