Corporate Medical Policy

Amniotic Membrane and Amniotic Fluid Injections for Ophthalmic Indications

File Name: amniotic_membrane_and_amniotic_fluid_injections_for_ophthalmic_indications
Origination: 7/2016
Last Review: 6/2024

Description of Procedure or Service

This policy only addresses amniotic membrane and amniotic fluid injections for ophthalmic indications. This policy does not address the use of amniotic products for usage in wounds or burns. Please see related policy for wound and burn indications.

Human amniotic membrane (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. 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 d-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.

HAM is an established treatment for corneal reconstruction and is being evaluated for the treatment of various conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures. Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for a wide variety of conditions.

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. The fluid contains proteins, carbohydrates, proteins and 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. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubrican, 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. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. .

Amniotic Membrane and Amniotic Fluid Injections for Ophthalmic Indications

Related policies:
Skin and Soft Tissue Substitutes
Growth Factors in Wound Healing
Meniscal Allograft and Collagen Meniscus Implants
Orthopedic Applications of Stem Cell Therapy
Plugs for Fistula Repair

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for human amniotic membrane when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met.

Injection of human amniotic fluid is considered investigational for all indications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Amniotic Membrane and Amniotic Fluid Injections for Ophthalmic Indications are covered

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

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see Policy Guidelines);
- Corneal ulcers and melts that do not respond to initial conservative therapy (see Policy Guidelines);
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
- Bullous keratopathy as a palliative measure in patient who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty);
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;
- Moderate or severe Stevens-Johnson syndrome;
- Persistent epithelial defects that do not respond to conservative therapy (see Policy Guidelines);
- Severe dry dye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Septs 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines);
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue may be considered medically necessary for the treatment of the following ophthalmic indications:

- Corneal perforation when corneal tissue is not immediately available; or
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

When Amniotic Membrane and Amniotic Fluid Injections for Ophthalmic Indications are not covered

Human amniotic membrane grafts with or without suture are considered investigational for all ophthalmic indications not outlined above.

Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis.

Injection of human amniotic fluid is considered investigational for all indications.

All other human amniotic membrane products and indications not listed above are considered investigational. For wound and burn indications, please see related policy "Skin and Soft Tissue Substitutes."

Policy Guidelines

Conservative therapy for neurotrophic keratitis may include 5 days of pressure patching, therapeutic contact lens, topical lubricants, and topical antibiotics.

Conservative therapy for corneal ulcers and melts may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents.

A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment of a persistent epithelial defect may include 5 days of the following: topical lubricants, topical antibiotics, therapeutic contact lens, or patching.

Tear Film and Ocular Surface Society staged management for dry eye diseases
Step 1:

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

Step 2:
If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands

- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

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

Summary of Evidence:

Ophthalmic Conditions

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

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. 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. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Ulcers and Melts That does not Respond to Initial Medical Therapy

For individuals who have corneal ulcers and melts, that does not respond to initial medical therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Bullous Keratopathy as a Palliative Measure in Patients Who are not Candidates for a Curative Treatment (eg, endothelial or penetrating keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Partial 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 RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Stevens-Johnson Syndrome

For individuals who have moderate or severe Stevens-Johnson syndrome 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 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease, supported the use of HAM for moderate or severe Stevens-Johnson. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Persistent Epithelial Defects and Ulceration That 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 RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulcerations that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. 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. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 65778, 65779 and 65780

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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

Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. Oct 2013;34(10):1332-1339. PMID 23945520

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149. 2/11/2016

Medical Director Review 9/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 1/12/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 5/8/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 2/8/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 2/14/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 2/13/2020

Specialty Matched Consultant Advisory Panel 8/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.149, 2/11/2021

Specialty Matched Consultant Advisory Panel 6/2021

Medical Director review 6/2021

Specialty Matched Consultant Advisory Panel 6/2022

Medical Director review 6/2022

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

McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328

American Academy of Ophthalmology - Preferred Practice Patterns - Dry Eye Syndrome, 2018 https://www.aao.org/education/preferred-practice-pattern/dry-eye-syndrome-ppp-2018

Specialty Matched Consultant Advisory Panel 6/2023

Medical Director review 6/2023

American Academy of Ophthalmology - Preferred Practice Patterns - Dry Eye Syndrome, 2018 https://www.aao.org/education/preferred-practice-pattern/dry-eye-syndrome-ppp-2018. Accessed May 29, 2024.

U.S. Food and Drug Administration. 510(k) Summary: ProKeraTM Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed January 3, 2024.

American Academy of Ophthalmology - Preferred Practice Patterns - Dry Eye Syndrome, 2023 https://www.aao.org/education/preferred-practice-pattern/dry-eye-syndrome-ppp-2018. Accessed May 30, 2024.

Specialty Matched Consultant Advisory Panel 6/2024

Medical Director review 6/2024

Policy Implementation/Update Information

7/26/16 New policy developed. Injection of micronized amniotic membrane or amniotic fluid is considered investigational for all indications. See also policy titled "Bioengineered Skin and Tissue." (an)

10/25/16 Specialty Matched Consultant Advisory Panel review 9/28/2016. Policy accepted as written. (an)

2/24/17 Description section extensively revised. Policy statement revised: "**BCBSNC will provide coverage for human amniotic membrane when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met."** Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary: AmnioBand® Membrane, Biovance®, Epifix®, Grafix™. All other human amniotic membrane products (micronized or particulated human amniotic membrane or human amniotic fluid) for any other indications are considered investigational. Policy Guidelines section updated. Coding/Billing section updated to include codes and coding instructions. (an)

4/28/17 Following statement added to the When Covered section: application of Epifix is limited to no more than 5 weekly applications per wound. (This statement was moved out of the Bioengineered Skin medical policy and into this policy). (an)

6/30/17 Sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: Neurotrophic keratitis, Corneal ulcers and melts, Pterygium repair, Stevens-Johnson syndrome, Persistent epithelial defects. Sutured human amniotic membrane grafts are considered investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy. Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is investigational. Policy Guidelines updated. Codes 65778, 65779 added to Billing/Coding section. Reference added. **Notification given 6/30/17 for policy effective date of 9/29/17.** (an)

12/15/17 Codes added to Billing/Coding section effective 1/1/2018: Q4177, Q4178, Q4181. (an)

3/29/18 Revised 2 statements in the "When Not Covered" to read: 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 and All other human amniotic membrane products and indications not listed above are considered investigational, including but not limited to treatment of lower extremity ulcers due to venous insufficiency. Reference added. (an)

9/7/18 Specialty Matched Consultant Advisory Panel review 8/22/2018. No change to policy statement. (an)

7/1/19 Revised list of indications for when human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) may be considered medically necessary. Epicord added to list of medically necessary products for treatment of nonhealing diabetic lower-extremity ulcers. Updated Policy Guidelines. Code Q4131 deleted. Codes added to Billing/Coding section: *Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4202.* Reference added. (an)

9/10/19 Specialty Matched Consultant Advisory Panel 8/20/2019. Verbiage added to "when covered" and "when not covered" section "**With the exception of products used within the scope of FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational.**" (eel)

10/1/19 Coding section updated with new codes effective 10/1/19. Added codes *Q4205, Q4206, Q4208 – Q4221.* (eel)

6/30/20 Coding section updated with new codes effective 7/1/20. Added codes *Q4227 – Q4242, Q4244 – Q4248.* (eel)

9/8/20 Policy name updated from **Amniotic Membrane and Amniotic Fluid Injections** to **Amniotic Membrane and Amniotic Fluid Injections for Ophthalmic Indications**. Removed amniotic products related to burn and wound treatment from policy, Removed statement from "When covered" and "When not covered" sections related to rare skin conditions. Coding and Policy guidelines sections updated. Specialty Matched Consultant Advisory Panel review 8/19/2020. (eel)

7/13/21 Specialty Matched Consultant Advisory Panel review 6/16/2021. Reference added. Medical Director review. No change to policy statement. (lpr)

7/26/22 Specialty Matched Consultant Advisory Panel review 6/2022. Medical Director review 6/2022. No change to policy statement. (lpr)

7/18/23 Specialty Matched Consultant Advisory Panel review 6/21/2023. References added. Medical Director review 6/2023. (lpr)

7/17/24 Specialty Matched Consultant Advisory Panel review 6/19/2024. Medical Director review 6/2024. References added. No change to policy statement. (lpr)