

MEDICAL POLICY – 7.01.583

Amniotic Membrane and Amniotic Fluid

BCBSA Ref. Policy: 7.01.149

Effective Date: May 1, 2021

Last Revised: April 13, 2021

Replaces: N/A

RELATED MEDICAL POLICIES:


2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

7.01.113 Bioengineered Skin and Soft Tissue Substitutes

8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)

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Introduction

The amniotic membrane and amniotic fluid are structures that surround the fetus in the uterus (womb). The fluid protects the fetus from injury. The membrane is a thin mesh of protein and contains growth factors, stem cells, and other items crucial to a developing fetus. Processing and then using the amniotic membrane and/or fluid (after delivery), has been proposed to treat a number of conditions in adults. High quality medical studies show that using specific amniotic membrane products may be useful for treating diabetic ulcers in some cases, for specific eye conditions, and for a disorder known as Stevens-Johnson syndrome. This policy describes when these products may be considered medically necessary. Using amniotic membrane for other conditions or using amniotic fluid products is considered unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Medical Necessity
<p>Treatment of nonhealing diabetic lower-extremity ulcers</p>	<p>Treatment of nonhealing* diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary:</p> <ul style="list-style-type: none"> • Affinity® • AmnioBand® Membrane • Biovance® • EpiCord® • Epifix® • Grafix® <p>*Note: Nonhealing 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 (eg, Zelen et al, 2015).</p> <p>When the above medical necessity criteria are met, the following conditions of coverage will apply:</p> <ul style="list-style-type: none"> • Treatment is limited to a maximum of 6 applications in 12 weeks when evidence of wound healing is present <p>Graft applications that exceed what is reasonable and necessary as size-appropriate based on the size of the wound are considered not medically necessary (see Related Information).</p> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>
<p>Human amniotic membrane grafts for ophthalmic indications</p>	<p>Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) may be considered medically necessary for the treatment of the following ophthalmic indications:</p> <ul style="list-style-type: none"> • Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty)



Service	Medical Necessity
	<ul style="list-style-type: none"> • Corneal ulcers and melts that do not respond to initial conservative therapy (see Definition of Terms) • Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment • Moderate or severe acute ocular chemical burn • Moderate or severe Stevens-Johnson syndrome • Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see Definition of Terms) • Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient • Persistent epithelial defects that do not respond to conservative therapy (see Definition of Terms) • 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 Related Information) <p>Human amniotic membrane grafts with suture or glue may be considered medically necessary for the treatment of the following ophthalmic indications:</p> <ul style="list-style-type: none"> • Corneal perforation when corneal tissue is not immediately available; <p>OR</p> <ul style="list-style-type: none"> • Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft

Service	Investigational
Human amniotic membrane for other ophthalmic indications	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	<p>Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of:</p> <ul style="list-style-type: none"> • osteoarthritis • plantar fasciitis



Service	Investigational
Injection of human amniotic fluid	Injection of human amniotic fluid is considered investigational for all indications.
Other indications	All other indications not listed above are considered investigational, including but not limited to treatment of lower extremity ulcers due to venous insufficiency.

Investigational		
All other human amniotic membrane products not listed above are considered investigational, including but not limited to:		
<ul style="list-style-type: none"> • AlloGen® liquid • AlloWrap® DS or dry • AltIPly™ • AmnioAMP-MP™ • Amnioarmor™ • AmnioBand® Particulate • Amniocore™ • Amniocyte™ • Amniocyte plus™ • Amnioexcel® • Amnioexcel® plus • Amnio-maxx™ • Amnio-maxx lite™ • AmnioMatrix® injectable • Amnion Bio • Amniorepair® • Amniotext® • Amniotext patch • Amnio Wound • Amnio Wrap2™ • AmniPLY® • Artacent® AC (flowable) • Artacent® AC (patch) • Artacent® Cord • Artacent® Wound • Ascent • Axobiomembrane • Axolotl Ambient® • Axolotl Cryo® • Axolotl DualGraft™ 	<ul style="list-style-type: none"> • carePATCH • Cellesta™ • Cellesta™ Cord • Cellesta™ Duo • Cellesta™ flowable amnion injectable • Clarix 100 • Clarix® Cord 1K • ClarixFlo® • Cogenex flowable amnion • Cogenex amniotic membrane • Corecyte™ • Corplex • Corplex P • Coretext™ • Cryo-cord™ • Cygnus™ • Dermacyte® • Dermavest® • Derm-maxx • Epifix Injectable • FlowerAmnioFlo® (liquid) • FlowerAmnioPatch • Fluid Flow™ liquid • Fluid GF liquid • Genesis amniotic membrane • Interfyl® • Keroxx® • Matrimon • Membrane Graft 	<ul style="list-style-type: none"> • Novachor™ • Novafix® • Novafix® DL • Nudyn® • NuShield® • PalinGen® Membrane • PalinGen® XPlus • PalinGen® SportFlow • Plurivest™ • ProMatrX liquid • Polycyte™ • Procenta® • Protect™ • Reguard • Restorigin™ • Restorigin™ Injectable • Revita® • Revitalon™ • Surfactor® • Surgenex, • SurgiCORD • SurGraft® • SurgiGRAFT™ • SurgiGRAFT™-DUAL • Therion • WoundEx® • WoundEx® Flow • WoundFix™ • WoundFix™ Plus • WoundFix™ Xplus



<ul style="list-style-type: none"> • Axolotl Graft™ • Biodexcel • BioDFence® • BioDFence® DryFlex® • BioDMatrix injectable • BioNext® PATCH • BioSkin® • BioSkin® Flow • BioWound™ • BioWound™ Plus • BioWound™ Xplus 	<ul style="list-style-type: none"> • Membrane Wrap • NeoPatch® • Neox® 100 • Neox™ Cord 1k • Neox® Cord-RT • Neox® Flo • Neox® Wound 	<ul style="list-style-type: none"> • Xcellerate™ • Xwrap®
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Note: HRT: Human Regenerative Technologies; MTF Musculoskeletal Transplant Foundation ^a Processed by HRT and marketed under different tradename

Documentation Requirements

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Name of product to be used
- Previous therapy attempted and for how long

Coding

Code	Description
HCPCS	
Reviewed for Medical Necessity	
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter
Q4145	EpiFix®, injectable, 1 mg
Q4151	AmnioBand® or Guardian, per sq cm
Q4154	Biovance®, per sq cm
Q4159	Affinity®, per sq cm



Code	Description
Q4168	AmnioBand®, 1 mg
Q4186	Epifix®, per square centimeter
Q4187	EpiCord®, per square centimeter
Investigational (Not Eligible for Coverage)	
Q4100	Skin substitute, not otherwise specified)
Q4137	AmnioExcel®, AmnioExcel® Plus or Biodexcel, per sq cm
Q4138	BioDFence® DryFlex, per sq cm
Q4139	AmnioMatrix® or BioDMatrix, injectable, 1 cc.
Q4140	BioDFence®, per sq cm
Q4148	Neox™ Cord 1k, Neox® Cord RT, or Clarix® Cord 1K, per sq cm
Q4150	AlloWrap® DS or dry, per square centimeter
Q4153	Dermavest® and Plurivest™, per sq cm
Q4155	Neox® Flo or Clarix Flo®, 1 mg
Q4156	Neox® 100 or Clarix 100, per sq cm
Q4157	Revitalon™, per sq cm
Q4160	Nushield®, per sq cm
Q4162	WoundEx® Flow, BioSkin® Flow, 0.5 cc
Q4163	WoundEx®, BioSkin®, per sq cm
Q4169	Artacent® wound, per sq cm
Q4170	Cygnus™per sq cm
Q4171	Interfyl®, 1 mg
Q4173	PalinGen® or PalinGen® XPlus, per sq cm
Q4174	PalinGen® or ProMatrX, 0.36 mg per 0.25 cc
Q4176	Neopatch or therion, per square centimeter
Q4177	FlowerAmnioFlo®, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm



Code	Description
Q4180	Revita®, per sq cm
Q4181	Amnio Wound, per sq cm
Q4183	SurgiGRAFT™, per square centimeter
Q4184	Cellesta™ or Cellesta™ Duo, per square centimeter
Q4185	Cellesta™ flowable amnion (25 mg per cc); per 0.5 cc
Q4188	AmnioArmor™, per square centimeter
Q4189	Artacent® AC, 1 mg
Q4190	Artacent® AC, per square centimeter
Q4191	Restorigin™, per square centimeter
Q4192	Restorigin™, 1 cc
Q4194	Novachor™, per square centimeter
Q4198	Genesis Amniotic Membrane, per square centimeter
Q4201	Matrion, per sq cm
Q4202	Keroxx ® (2.5 g/cc), 1 cc
Q4204	XWRAP, per square centimeter
Q4205	Membrane Graft or Membrane Wrap, per sq cm
Q4206	Fluid Flow™ or Fluid GF, 1 cc
Q4208	Novafix®, per sq cm
Q4209	SurGraft®, per sq cm
Q4210	Axolotl Graft® or Axolotl DualGraft®, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	AlloGen®, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord™, per sq cm
Q4215	Axolotl Ambient® or Axolotl Cryo®, 0.1 mg
Q4216	Artacent® Cord, per sq cm



Code	Description
Q4217	WoundFix™, BioWound™, WoundFix™ Plus, BioWound™ Plus, WoundFix™ Xplus or BioWound™ Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT™-DUAL, per sq cm
Q4221	Amnio Wrap2™, per sq cm
Q4227	AmnioCore™ per sq cm (new code effective 7/1/20)
Q4228	BioNext® PATCH, per sq cm (new code effective 7/1/20)
Q4229	Cogenex Amniotic Membrane, per sq cm (new code effective 7/1/20)
Q4230	Cogenex Flowable Amnion, per 0.5 cc (new code effective 7/1/20)
Q4231	Corplex P, per cc (new code effective 7/1/20)
Q4232	Corplex, per sq cm (new code effective 7/1/20)
Q4233	SurFactor® or NuDyn®, per 0.5 cc (new code effective 7/1/20)
Q4234	XCellerate™, per sq cm (new code effective 7/1/20)
Q4235	AMNIOREPAIR® or AltiPly™, per sq cm (new code effective 7/1/20)
Q4236	carePATCH, per sq cm (new code effective 7/1/20)
Q4237	Cryo-Cord™, per sq cm (new code effective 7/1/20)
Q4239	Amnio-Maxx™ or Amnio-Maxx™ Lite, per sq cm (new code effective 7/1/20)
Q4240	CoreCyte™, for topical use only, per 0.5 cc (new code effective 7/1/20)
Q4241	PolyCyte™, for topical use only, per 0.5 cc (new code effective 7/1/20)
Q4242	AmnioCyte Plus™, per 0.5 cc (new code effective 7/1/20)
Q4244	Procenta®, per 200 mg (new code effective 7/1/20)
Q4245	AmnioText®, per cc (new code effective 7/1/20)
Q4246	CoreText™ or ProText™, per cc (new code effective 7/1/20)
Q4247	Amniotext patch, per sq cm (new code effective 7/1/20)
Q4248	Dermacyte® Amniotic Membrane Allograft, per sq cm (new code effective 7/1/20)
Q4249	MNIPLY®, for topical use only, per square centimeter (new code effective 10/1/20)
Q4250	AmnioAmp-MPMP™, per square centimeter (new code effective 10/1/20)



Code	Description
Q4254	Novafix® DL, per square centimeter (new code effective 10/1/20)
Q4255	REGUaRD, for topical use only, per square centimeter (new code effective 10/1/20)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Definition of Terms

Persistent epithelial defect: A defect 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.

Conservative treatment: The 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 human amniotic membrane grafts. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regarding treatments requiring multiple drops per day.

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.

Tear Film Break-up Time (TFBUT): The interval between the last complete blink and the first appearance of a dry spot, or disruption in the tear film after fluorescein has been instilled onto the bulbar conjunctiva and observed with a slit-lamp with the person staring straight ahead without blinking. A stop watch is used to record the time between the last complete blink and the first appearance of a dry spot in the tear film. Less than 5 seconds indicates a dry eye; greater than 5 seconds is considered normal.

Schirmer's Test: Filter paper is placed inside the lower eyelid of both eyes and the person then closes their eyes for 5 minutes. Afterwards, the filter paper is assessed to see how far the tears have travelled on the paper. A measurement of less than 5 mm is considered a severely dry eye.



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
 - 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)

Table 1. Dry Eye Severity Level Dry Eye Workshop Score (DEWS) 3 to 4

Dry Eye Severity Level	3	4
Discomfort, severity & frequency	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	+ / -	+ / ++
Conjunctival staining	Moderate to marked	Marked
Corneal staining (severity/location)	Marked central	Severe punctate erosions



Dry Eye Severity Level	3	4
Corneal/tear signs	Filamentary keratitis, mucus clumping, increasing tear debris	Filamentary keratitis, mucus clumping, increasing tear debris, ulceration
Lid/meibomian glands	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (tear film break up test) (sec)	≤5	Immediate
Schirmer score (mm/5 min)	≤5	≤2

Source: https://www.tearfilm.org/dewsreport/pdfs/Definition%20and%20Classification%20of%20Dry%20Eye%20Disease_.pdf (p. 88 of document/p. 14 of PDF) (Accessed April 20, 2021).

Epifix® Sizing Guidelines

The allograft is intended for single-patient use only. All unused material should be discarded. Multiple sizes are available in a wide range of sheet and mesh configurations covering wounds. To determine the measure of a wound in square centimeters multiply the length of the wound by the width of the wound in centimeters. (eg, 10 cm in length x 5 cm in width = 50 cm²)

Here is a sample of the package standard sizes for Epifix:

Table 2. Epifix® Sample of Package Standard Sizes

Item Number	Size & Description	
GS-5024	24 mm disk	
GS-5330	3 cm x 3 cm sheet (9 sq cm)	
GS-5350	3 cm x 5 cm sheet (15 sq cm)	
GS-5460	4 cm x 6 cm sheet (24 sq cm)	
GS-5560	5 cm x 6 cm sheet (30 sq cm)	
GS-5770	7 cm x 7 cm sheet (49 sq cm)	
ES-3500	3 cm x 5 cm mesh sheet (15 sq cm)	
ES-4400	4 cm x 4.5 cm mesh sheet (18 sq cm)	
ES-5500	5 cm x 5.5 cm mesh sheet (27.5 sq cm)	

Source: <https://mimedx.com/epifix/> (Accessed April 20, 2021).



Table 3. AmnioBand® Sizing Guidelines

Tissue Code	Product Specifications
WC3010	AmnioBand Membrane, 10mm Disk
WC3014	AmnioBand Membrane, 14mm Disk
WC3016	AmnioBand Membrane, 16mm Disk
WC3018	AmnioBand Membrane, 18mm Disk
WC3022	AmnioBand Membrane, 2cm x 2cm
WC3023	AmnioBand Membrane, 2cm x 3cm
WC3024	AmnioBand Membrane, 2cm x 4cm
WC3034	AmnioBand Membrane, 3cm x 4cm
WC3044	AmnioBand Membrane, 4cm x 4cm
WC3038	AmnioBand Membrane, 3cm x 8cm
WC3046	AmnioBand Membrane, 4cm x 6cm
WC3056	AmnioBand Membrane, 5cm x 6cm
WC3077	AmnioBand Membrane, 7cm x 7cm

Source: <https://www.mtfbiologics.org/our-products/detail/amnioband-membrane> (Accessed April 20, 2021).

Table 4. Other Product Size Specifications

Name	Available Sizes	Link
Affinity	1.5 x 1.5 cm (2.25 square cm) 2.5 x 2.5 cm (6.25 square cm)	https://affinityfresh.com/why-choose-affinity/product-details-and-resources.html
Biovance®	1 x 2 cm 2 x 2 cm 2 x 3 cm 2 x 4 cm 3 x 3.5 cm 4 x 4 cm 5 x 5 cm 6 x 6 cm	https://www.biovance.net/ordering-information.html
Epicord®	2 cm x 3 cm (6 sq cm) 3 cm x 5 cm (15 sq cm)	https://mimedx.com/epicord/ (see product details, other information)
Grafix®	16 mm 1.5 cm x 2 cm 2 cm x 3 cm	http://www.osiris.com/grafix/healthcare-professionals/



Name	Available Sizes	Link
	3 cm x 4 cm 5 cm x 5 cm	

Evidence Review

Description

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.

Background

Human Amniotic Membrane

Human amniotic membrane (HAM) consists of 2 conjoined layers, the amnion and chorion, and forms the innermost lining of the amniotic sac or placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. Many products available using amnion, chorion, amniotic fluid, and umbilical cord are being studied for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions. The products are formulated either as patches, which can be applied as wound covers, or as suspensions or particulates, or connective tissue extractions, which can be injected or applied topically (see [Table 5](#)).

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.¹ There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered to be non-immunogenic and has not been observed to cause substantial immune response. It is believed that these properties are retained in cryopreserved HAM (C-HAM) and dehydrated HAM (D-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.²

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures.¹ Additional indications studied in pre-clinical 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 a separate policy (see [Related Medical Policies](#)).

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes randomized controlled trials



(RCTs). The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The RCTs evaluating amniotic and placental membrane products for the treatment of nonhealing (<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 (ITT) analysis. For the HAM products that have been sufficiently evaluated (ie, 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 quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes two multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at four weeks did not differ between EpiFix and the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but 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 that the technology results in an improvement in the nethealth outcome.

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, quality of life, and treatment-related morbidity. The pilot study assessed the feasibility of a larger RCT evaluating HAM injection. Additional trials, which will have a larger sample size and longer follow-up, are needed to permit



conclusions on the effect of this treatment. The evidence is insufficient to determine that the technology results in an improvement in the nethealth outcome.

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 that the technology results in the nethealth outcome.

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 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 quality of life. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see [Clinical Input](#) below)

Corneal Ulcers and Melts that Does Not Respond to Initial Medical Therapy

For individuals who have corneal ulcers and melts that do 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and 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 22 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 an 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 quality of life. No comparative evidence was identified for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see [Clinical Input](#) below)

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 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. (see [Clinical Input](#) below)

Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is Not Sufficient

For individuals who have partial limbal stem cell deficiency (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 quality of life. No



comparative trials 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see [Clinical Input](#) below)

Moderate or Severe Stevens-Johnson Syndrome

For individuals who have moderate or severe Stevens-Johnson syndrome (SJS) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome includes one RCT with 25 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, thus supporting the use of HAM for moderate or severe Stevens-Johnson. 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 do not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. (see [Clinical Input](#) below)

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 do 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 quality of life. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as three months. The evidence is



sufficient to determine that the technology results in an 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 three RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes an RCT of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the three RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.(see [Clinical Input](#) below)

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 quality of life. 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 quality of life. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. (see [Clinical Input](#) below)



Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in [Table 5](#).

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03414268^a	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Plantar Fasciitis	276	Apr 2021
NCT02982226^a	A Comparative Study of Injectable Human Amniotic Allograft (ReNu™) Versus Corticosteroids for Plantar Fasciitis: A Prospective, Randomized, Blinded Study	150	Apr 2021
NCT03414255^a	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial Of The Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Achilles Tendonitis	158	May 2021
NCT03485157^a	A Phase 2B, Prospective, Double-blinded, Randomized Controlled Trial of the Micronized Dehydrated Human Amnion Chorion Membrane Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee	466	Oct 2021
NCT04457752^a	A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers	124	Dec 2021
NCT03390920	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jun 2022
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
NCT04553432^a	Dry Eye OmniLenz Application of Omnigen Research Study	70	Jul 2022
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear	100	Sep 2022



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04636229^a	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	474	Dec 2023
NCT03864939	Randomized Pilot Study to Improve Postprostatectomy Incontinence and Potency by Application of Dried Human Amnion Graft	328	Apr 2025
Unpublished			
NCT02609594^a	A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers	240	Dec 2018 (status unknown)
NCT02838784^a	The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study	134	Dec 2018 (status unknown)
NCT03441607^a	Safety & Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane)® in Adults With Pain Due to Osteoarthritis of the Knee	320	Mar 2019 (status unknown)
NCT02318511^a	An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	200	Feb 2019 (completed)
NCT03379324^a	A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft	260	Sep 2019 (status unknown)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.



2019 Input

In response to requests while this policy was under review in 2018-2019, clinical input on the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Evidence from clinical input is integrated within the [Summary of Evidence](#) section.

Clinical input was sought to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Clinical input supported the use of amniotic membrane in individuals with the following indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) as an alternative to stromal puncture.
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Persistent epithelial defects and ulcerations that do not respond to conservative therapy.
- Severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.



- Moderate or severe acute ocular chemical burn.
- Corneal perforation when corneal tissue is not immediately available.
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Practice Guidelines and Position Statements

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.³⁹ The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, “healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.” References from two randomized controlled trials on dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

Tear Film and Ocular Surface Society

In 2017, The Tear Film and Ocular Surface Society published the Dry Eye Workshop II (DEWS) management and therapy report.²³ The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

- 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)

Society for Vascular Surgery et al

In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."⁴⁰

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

The U.S. Food and Drug Administration (FDA) 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:

- "The HCT/P is minimally manipulated;
- The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- 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 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
- Either:
 - 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
 - The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 - Is for autologous use;
 - Is for allogeneic use in a first-degree or second-degree blood relative; or
 - Is for reproductive use."

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

- "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.
- 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.
- 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.

References

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 <https://www.regulations.gov/document?D=FDA-2017-D-6146-0003> Accessed April 20, 2021.
5. Food and Drug Administration. 510(k) Summary: ProKera™ Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed April 20, 2021.
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 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 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 DRy Eye Amniotic Membrane (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
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. 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
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

History

Date	Comments
08/01/20	New policy, approved July 14, 2020. Policy replaces 7.01.149. AmnioFix added as investigational. All other policy statements remain unchanged.



Date	Comments
10/01/20	Coding update. Added HCPCS codes Q4249, Q4250, Q4254, Q4255.
05/01/21	Annual Review, approved April 13, 2021. Policy updated with literature review through December 28, 2020; references added. Affinity added to medically necessary statement for the treatment of diabetic foot ulcers; edits made to investigational statement on human amniotic products.

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You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፈላጊ እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታወቅ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):

Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):

Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈໍາເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងរបស់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ដុល្លារចេញផ្លូវ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیر بران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).