Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 06/12/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Recombinant and Autologous Platelet Derived Growth Factors for Wound Healing and Other Non Orthopedic Conditions is addressed separately in medical policy 00262.

Note: Bioengineered Skin and Soft Tissue Substitutes is addressed separately in medical policy 00572.

Note: Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow) is addressed separately in medical policy 00258.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider treatment of nonhealing and not clinically infected diabetic foot ulcers using the following human amniotic membrane (HAM) products (Affinity®, AmnioBand® Membrane, Biovance®, EpiCord®, Epifix®, Grafix™)‡ to be **eligible for coverage**** when the following criteria are met:

- Initial treatment may be approved for up to 4 applications over 6 weeks period per nonhealing wound that is not infected and patient agrees to comply with adequate mechanical offloading (see Policy Guidelines); or
- Additional applications after initial 6 weeks may be eligible for coverage when following criteria are met:
    - Documented objective evidence of wound healing (e.g. development and presence of healthy granulation tissue with progressive wound contracture or decreasing depth); and

- Approved HAM product is applied no more frequently than in one-week intervals; and
- Patient remains compliant with adequate mechanical offloading; and
- Continued treatment may be approved for up to 4 additional applications over 6 more weeks, per wound treated.

Based on review of available data, the Company may consider HAM grafts with or without suture or glue (e.g., Prokera®, AmbioDisk™, AmnioGraft®, Artacent Ocular, Vendaje Optic™)‡ for the treatment of any of the following ophthalmic indications to be **eligible for coverage:****

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

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers injection of micronized or particulated human amniotic membrane for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis.to be **investigational.***

Based on review of available data, the Company considers human amniotic membrane grafts with or without suture for all ophthalmic indications not outlined above to be **investigational.***

Based on review of available data, the Company considers injection of human amniotic fluid for all indications to be **investigational.***

Based on review of available data, the Company considers all other human amniotic products (eg, derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above to be **investigational.***

Based on review of available data, the Company considers use for all other indications not listed above to be **investigational*** including but not limited to:

- Treatment of lower-extremity ulcers due to venous insufficiency
- Repair following Mohs micrographic surgery
- When criteria above are not met including using more than 8 applications beyond 12 weeks for diabetic foot ulcers

Policy Guidelines

Non-healing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks, based on the entry criteria for clinical trials (eg, Zelen et al [2015]). Tables PG1 and PG2 list the medically necessary and investigational amniotic products that have an HCPCS code.

Table PG1 Amniotic Products Listed in the Policy Statements

Trade Name	Supplier	HCPCS Code
Affinity®‡	Organogenesis (previously NuTech Medical)	Q4159

AmnioBand®‡ Membrane	MTF Wound Care	Q4151
Biovance®‡	Celularity	Q4154
Epifix®‡	MiMedx	Q4186
Epicord®‡	MiMedx	Q4187
Grafix®‡	Osiris	Q4132, Q4133

Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Acesso dl, per square centimeter	Acesso DL by Dynamic Medical Services LLC, Surgenex. Per the manufacturer, this is a sterile dehydrated dual layered human amniotic membrane allograft intended to serve as a barrier or cover for acute and chronic wounds and for use as a barrier to protect wounds from the surrounding environment	Q4293
Acesso tl, per square centimeter	Acesso TL by Dynamic Medical Services LLC DBA Acesso Biologics, Surgenex. Per the manufacturer, this product is a triple layer sterile, single use, dehydrated allograft derived from	Q4300

	donated human placental birth tissue.	
Activate matrix, per square centimeter	Activate™ Matrix. Per the manufacturer, this product consists of three layers of the placental membranes including amnion, intermediate layer and chorion. It is a minimally manipulated human placental membrane product derived from donated placental tissues that retain the structural and functional characteristics of the tissues.	Q4301
Allogen	Vivex Biomedical	Q4212
AlloWrap™‡	AlloSource	Q4150
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™‡	Tissue Transplant Technology	Q4188
AmnioBand®‡ Particulate	MTF Wound Care	Q4168
AmnioExcel®‡	Derma Sciences	Q4137
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245

Amnio tri-core amniotic, per square centimeter	Amnio Tri-Core™ by Stability Biologics. Per the manufacturer, this is a three-layer allogeneic amniotic membrane allograft for use as a wound barrier and covering.	Q4295
Amnio quad-core, per square centimeter	Amnio Quad-Core by Stability Biologics. Per the manufacturer, this is is a four-layer allogeneic amniotic membrane allograft for use as a barrier and applied as a single use covering.	Q4294
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™‡	Stability Biologics	Q4227
Amniocore pro, per square centimeter	Amnio Core Pro by Stability Biologics. Per the manufacturer, this product is comprised of amniotic (inferior surface) and chorionic (superior surface) membrane. The addition of the chorion provides additional active angiogenic growth factors	Q4298

	compared to just amnion layers allografts.	
Amnicore pro+, per square centimeter	AmnioCore Pro+ by Stability Biologics. Per the manufacturer, this product is an exclusive and bioactive allograft different from AmnioCore Pro and other AmnioCore brands. The AmnioCore Pro+ is a three-layer allograft comprised of amniotic membrane and chorionic membrane. The amnion is the inferior surface, chorion is the inner layer, and there is another amnion superior surface. The addition of the chorion provides additional active angiogenic growth factors compared to just amnion and the extra tissue layer provided a significant increase in tensile strength	Q4299
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix®‡	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235

Amniotext patch	Regenerative Labs	Q4247
AmnioWrap2™‡	Direct Biologics	Q4221
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent®‡ Wound	Tides Medical	Q4169
Artacent®‡ Cord	Tides Medical	Q4126
Ascent	StimLabs	Q4213
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
BioDDryFlex®‡	BioD	Q4138
BioDfence™‡	Integra Life Science	Q4140
BioNextPATCH	BioNext Solutions	Q4228
BioWound, BioWound Plus™‡, BioWound XPlus™‡	HRT[a]	Q4217
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
Clarix®‡	Amniox Medical	Q4156
Clarix®‡ Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Complete aa, per square centimeter	Complete™ AA by Samaritan Biologics LLC.	Q4303

	Per the manufacturer, this is a dual layer amnion derived allograft that serves as a barrier and provide protective coverage from the surrounding environment to acute and chronic wounds. Complete™ AA is a sterile, single use, dehydrated allograft derived from donated human amnion membrane.	
Complete aca, per square centimeter	Complete™ ACA by Samaritan Biologics LLC. Per the manufacturer, this is a a three-layer amnion-chorion-amnion derived allograft to serve as a barrier and provide protective coverage from the surrounding environment to acute and chronic wounds.	Q4302
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237

Cygnus	Vivex Biomedical	Q4170
Dermacyte	Merakris Therapeutics	Q4248
Dermabind ch, per square centimeter	DermaBind CH™ by Health Tec Wound Care. Per the manufacturer, this is a dehydrated human chorion-derived membrane allograft comprised of an extracellular matrix that is rich in collagen, fibrin, and elastin fibers native to the tissue. It is designed for application directly to acute and chronic wounds, is flexible, and is a conforming cover that adheres to complex anatomies.	Q4288
Dermabind dl, per square centimeter	DermaBind DL™ by Health Tec Wound Care. Per the manufacturer, DermaBind DL™ membrane is intended for use as a wound covering, providing protection for the wound from the external environment and maintaining a moist environment.	Q4287
Dermavest™‡ or Plurivest	AediCell[a]	Q4153

Derm-maxx	Royal Biologics	Q4238
Emerge matrix, per square centimeter	Emerge™ Matrix by Sequence LifeScience, Inc. Per the manufacturer, this is a dual membrane, minimally manipulated, human amniotic and chorionic membrane product derived from placental tissue that retain the structural and functional characteristics of the tissue. The final product is dehydrated, packaged in different size sheets, and terminally sterilized by irradiation. Emerge™ Matrix consist primarily of extracellular matrix proteins and serves as a natural, biologic barrier or wound cover.	Q4297
Epifix Injectable	MiMedx	Q4145
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Grafix plus, per square centimeter	Per the manufacturer, this is a lyophilized human	Q4304

	placental chorionic membrane based skin substitute product. GRAFIX PLUS is indicated for use in the treatment of acute and chronic wounds.	
Guardian/AmnioBand®‡	MTF Wound Care	Q4151
Interfyl®‡	Celularity	Q4171
Lamellas, per square centimeter	Lamellas by Keyport Management. Per the manufacturer, Lamellas Membrane is intended for use as a protective wound covering and barrier in acute and chronic wounds. Lamellas Membrane is a sterile, single use, dehydrated resorbable allograft derived from donated human placental birth tissue.	Q4292
Lamellas xt, per square centimete	Lamellas XT by Keyport Management. Per the manufacturer, is intended for use as a protective wound covering and barrier in acute and chronic wounds. Lamellas XT Membrane is a sterile, single use, dehydrated	Q4291

	resorbable allograft derived from donated human placental birth tissue.	
Matrion	LifeNet Health	Q4201
Membrane wrap-hydro, per square centimeter	Membrane Wrap-Hydro™ by BioLab Sciences. Per the manufacturer, this product is a hydrated human amnion membrane allograft that serves as protective covering from the surrounding environment for acute and chronic wounds.	Q4290
Neopatch or Therion	CryoLife	Q4176
Neox®‡ Cord	Amniox Medical	Q4148
Neox®‡ Flo	Amniox Medical	Q4155
Neox®‡ Wound	Amniox Medical	Q4156
Novachor	Organogenisis	Q4191
Novafix®‡	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuDYN®‡ DL MESH	Fida Pharma USA	Q4285
NuDYN®‡ SLW	Fida Pharma USA	Q4286
NuShield	Organogenesis	Q4160
PalinGen®‡ Membrane	Amnio ReGen Solutions	Q4173

PalinGen®‡ SportFlow	Amnio ReGen Solutions	Q4174
Plurivest™‡	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4244
Rebound matrix, per square centimeter	Rebound™ Matrix by Sequence LifeScience, Inc. Per the manufacturer, this is a full thickness minimally manipulated human placental membrane product derived from donated placental tissues. Rebound™ Matrix is composed of extracellular matrix proteins and serves as a natural, biological barrier or wound cover.	Q4296
Reguard	New Life Medical	Q4255
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™‡	Medline Industries	Q4157
Revoshield + amniotic barrier, per square centimeter	RevoShield + Amniotic Barrier by 4Front Strategic Partners, Surgenex, LLC. Per the	Q4289

	manufacturer, this is a minimally manipulated dual layer tissue-based product derived from the amniotic membrane of the human placenta. The intended use of the product is to serve as a barrier or to provide protective coverage from the surrounding environment for acute and chronic wounds.	
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT™‡	Synergy Biologics	Q4183
Vendaje ac, per square centimeter	VENDAJE AC™ by BioStem Technologies, Inc. Per the manufacturer, this is a decellularized human amniotic and chorionic allograft product derived from placental tissues. VENDAJE AC™ is intended for use as a protective covering for soft tissue wounds	Q4279
WoundEx®‡	Skye Biologics[a]	Q4163
WoundEx®‡ Flow	Skye Biologics[a]	Q4162

Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation
[a] Processed by HRT and marketed under different tradename

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)

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

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Background/Overview

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.

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 a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. 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. Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

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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. 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. 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. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.

FDA or Other Governmental Regulatory Approval

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

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

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

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

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

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

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

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

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

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Several commercially available forms of 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.

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (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 an 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 2 RCTs. 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 2 multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of individuals with complete wound closure at 4 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 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 net health 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. 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 net health 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 an improvement in the net health 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT of 30 individuals 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.

Corneal Ulcers and Melts That Do 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. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. The systematic review showed healing in 97% of individuals with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 individuals found more rapid and complete epithelialization and more individuals 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. 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.

Bullous Keratopathy as a Palliative Measure in Individuals 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 a RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some individuals 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.

Moderate or Severe Stevens-Johnson Syndrome
For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes a RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome (includes 1 RCT with 25 individuals [50 eyes]) found improved symptoms and function with HAM compared to medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Persistent Epithelial Defects and Ulceration That Do 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. 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.

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. 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 individuals and a retrospective series of 84 individuals (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in 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 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 individuals with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is Not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. 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 an 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. 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.

Repair Following Mohs Micrographic Surgery
For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amniotic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of individuals requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of individuals who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.97; 95% CI, 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (p<.0001). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
2019 Input
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.

Supplemental Information

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

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- 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
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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, amnionic 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."

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. 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)

Wound Healing Society
In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment. 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 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04457752[a]	A Randomized 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	Mar 2023
NCT03390920[a]	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jan 2030
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL 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	130	Jul 2024
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN®‡ Injection in Individuals With Rotator Cuff Tear	100	Sep 2022
NCT04636229[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Individuals With Osteoarthritis of the Knee	474	Dec 2023
Unpublished			

NCT03855514[a]	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield®‡ and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers	200	Dec 2021 (Recruiting)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 08/19/2015
Current Effective Date: 06/12/2023

08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. New policy.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. AmnioBand Membrane, Biovance, Epifix, Grafix considered medically necessary for diabetic foot ulcers; all other products and indications are investigational. Sutured amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Ophthalmic products added and discontinued product names removed from Table 1.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Investigational indications clarified.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. EpiCord add to medically necessary statement for diabetic lower extremity ulcers. Sutured and non-sutured amniotic membrane may be considered medically necessary for specified ophthalmic conditions.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added criteria for non healing diabetic ulcers.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. 60-day provider notification required as proposed changes will result in more restrictive coverage criteria. Effective date is 11/01/2020. Replaced “diabetic lower extremity ulcers” with “diabetic foot ulcers” in the eligible for coverage statement for treatment of nonhealing and not clinically infected diabetic

	foot ulcers. This change is proposed to make distinction/clarification between other lower extremity ulcers in diabetics and true non-healing diabetic foot ulcers. Added the requirement that "patient agrees to comply with adequate mechanical offloading" for initial placement and similarly for continued treatment eligible for coverage criteria for additional applications, adding that "patient remains compliant with adequate mechanical offloading". Revised the Policy Guidelines definition of non-healing diabetic wounds was revised to "an ulcer that fails to demonstrate > 50% wound area reduction after a minimum of 4 weeks of standard wound therapy." It replaces the previous definition that was worded as "fails to demonstrate 20% decrease in wound area with standard wound care for at least 2 weeks."
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Brought back for clarification.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. AmnioGraft, Vendaje Optic and Artacent Ocular was added as eligible for coverage for HAM grafts with or without suture or glue. Added new investigational statement for repair following Mohs micrographic surgery.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2023	Coding update
09/20/2023	Coding update
09/27/2023	Added NuDYN®‡ DL MESH and NuDYN®‡ SLW to the PG2 table listing investigational amniotic products that have an HCPCS code
01/01/2024	Table PG 2 updated due to new codes. Coding update: Add new HCPCS codes.

Next Scheduled Review Date: 05/2024

Coding

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Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 06/12/2023

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Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 06/12/2023

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	15271, 15275, 17999, 65778, 65779, 65780
HCPCS	A2001, A4100, Q4100, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150. Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4176, Q4177, Q4178, Q4179, Q4181, Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4199, Q4201, Q4204, Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221, Q4224, Q4225, Q4256, Q4257, Q4258, Q4259, Q4260, Q4261, Q4227, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4237, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246, Q4247, Q4248, Q4249, Q4250, Q4251, Q4252, Q4253, Q4254, V2790 Add codes effective 01/01/2023: Q4236, Q4262, Q4263, Q4264 Add codes effective 04/01/2023: Q4265. Q4266, Q4267, Q4268, Q4269, Q4270, Q4271 Add codes effective 07/01/2023: Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283, Q4284 Add codes effective 10/01/2023: Q4285, Q4286 Add codes effective 01/01/2024: Q4279, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, Q4304
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 06/12/2023

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.