



Louisiana

Amniotic Membrane and Amniotic Fluid

Policy # 00458

Original Effective Date: 08/19/2015

Current Effective Date: 05/16/2018

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.

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 diabetic lower-extremity ulcers using the following human amniotic membrane (HAM) products (AmnioBand[®] Membrane, Biovance[®], Epifix[®], Grafix[™])[†] to be **eligible for coverage**.

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

Based on review of available data, the Company may consider sutured HAM grafts for the treatment of any of the following ophthalmic indications to be **eligible for coverage**:

- Neurotrophic keratitis; or
- Corneal ulcers and melts; or
- Pterygium repair; or
- Stevens-Johnson syndrome; or
- Persistent epithelial defects.

Note: *A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to human amniotic membrane grafts (AMGs). An AMG 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.*

When Services Are Considered Investigational

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

Based on review of available data, the Company considers sutured HAM grafts for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy to be **investigational**.*

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Based on review of available data, the Company considers HAM without suture (eg, Prokera[®], AmbioDisk[™])[‡] for ophthalmic indications to be **investigational**.*

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

Based on review of available data, the Company considers all other HAM products and indications not listed above, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency to be **investigational**.*

Background/Overview

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 1).

The fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause substantial immune response. It is believed that these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders.

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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.

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, lubricin, 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.

Table 1. Amniotic Membrane and Amniotic Fluid Preparations: Preparation and Components

Product (Supplier)	Preparation Cryopreserved, Dehydrated, or Extracted	Components			
		Amnion	Chorion	Amniotic Fluid	Umbilical Cord
Patch					
Affinity™ (NuTech Medical)	C	X			
AlloWrap™ (AlloSource)	NS	X			
AmbioDisk® (IOP Ophthalmics)	D				
AmbioDry5® (IOP Ophthalmics)	D				
AmnioBand® Membrane (MTF Wound Care)	D	X	X		
AmnioClear™ (Liventa Bioscience)	NS	X	X		
AmnioExcel® (Derma Sciences)	D	X			
AmnioFix® (MiMedx)	D	X			
AmnioGraft® (Bio-Tissue)	C	X			
Artacent® Wound (Tides Medical)	D	X			
BioDDryFlex® (BioD)	D	X			
BioDfence™ (BioD)	D	X	X		
BioSkin (HRT) ^a	D	X	X		
Biovance® (Alliqua Biomedical)	D	X			
Clarix® (Amnio Medical)	C	X			X
Cygnus (Vivex Biomedical)	D	X			
Cygnus Max (Vivex Biomedical)	D				X
EpiCord™ (MiMedx)	D				X
EpiFix® (MiMedx)	D	X	X		
Dermavest™ (Aedicell) ^a	C	X	X		X
Grafix® (Osiris)	C	X	X		
Guardian/AmnioBand® (MTF Wound Care)	D	X	X		
Neox® 100 (Amnio Medical)	C	X			X

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Product (Supplier)	Preparation	Components			
Neox® Cord (Amnio Medical)	C	X			X
Neox® Wound Allograft (Amnio Medical)	C	X			X
NuShield™ (NuTech Medical)	D	X	X		
PalinGen® Membrane (Amnio ReGen Solutions)	C	X			
Plurivest™ (Aedicell) ^a	C	X	X		X
Prokera® (Bio-Tissue)	C				
Revitalon™ (Medline Industries)	D	X	X		
WoundEx® (Skye Biologics) ^a	D	X	X		
Suspension, particulate, or extraction					
AmnioBand® Particulate (MTF Wound Care)	D	X	X		
AmnioMatrix® (Derma Sciences)	D	X		X	
AmnioVisc™ (Lattice Biologics)	NS			X	
BioSkin® Flow (HRT) ^b	E	X	X	X	X
Clarix® Flo (Amnio Medical)	C	X			X
Interfyl™ (Alliqua Biomedical)	NS	X	X		
Neox® Flo (Amnio Medical)	C	X			X
OrthoFlo™ (MiMedx)	D			X	
PalinGen® Flow (Amnio ReGen Solutions)	C	X		X	
PalinGen® SportFlow (Amnio ReGen Solutions)	C	X		X	
ProMatrX™ ACF (Amnio ReGen Solutions)	C	X		X	
ReNu™ (NuTech Medical)	D	X		X	
WoundEx® Flow (Skye Biologics) ^b	E	X	X	X	X

C: cryopreserved; D: dehydrated; E: extracted connective tissue; HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation; NS: not specified.

^{a,b} Processed by HRT and marketed by under different tradenames.

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.

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 (CFR) title 21, parts 1270 and 1271. Human amniotic membrane products and amniotic fluid products are included in these regulations.

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

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Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The primary end points of interest for trials of wound closure are as follows, consistent with guidance from the U.S. FDA for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).
3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.

DIABETIC LOWER-EXTREMITY ULCERS

Dehydrated Amniotic Membrane or Placental Membrane

AmnioBand vs Standard of Care

AmnioBand Membrane was compared with standard of care (SOC) for the treatment of nonhealing (minimum 4 weeks) diabetic foot ulcers in an industry-sponsored, multicenter trial by DiDomenico et al (2016). Forty patients were randomized to SOC or to SOC plus weekly applications of the dehydrated placental allograft for up to 12 weeks. Healing was determined by the principal investigator at each institution and confirmed by an independent and blinded panel of 6 physicians. This trial was adequately powered to detect a difference of 45% between groups in the primary outcome (the proportion of wounds

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healed at 6 weeks). Complete healing by 6 weeks was observed for 70% (14/20) of wounds treated with the dehydrated placental matrix compared with 15% (3/20) of wounds treated by SOC alone ($p=0.001$). The odds ratio for healing was 17 (95% confidence interval [CI], 3.1 to 93; $p=0.001$). At 12 weeks, complete healing was observed for 85% (17/20) of wounds in the AmnioBand group compared with 25% (5/20) in the SOC group. Mean time to heal for wounds treated with amniotic membrane was 36 days (95% CI, 27 to 46 days) compared with 70 days (95% CI, 59 to 81 days; $p<0.001$) with standard care. The number needed to treat to achieve healing at 12 weeks was 1.7 (95% CI, 1.2 to 2.8). Strengths of this trial included power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and intention-to-treat (ITT) analysis.

AmnioExcel vs Standard of Care

AmnioExcel dehydrated human amniotic membrane (d-HAM) was compared with SOC in an industry-sponsored, open-label multicenter RCT (N=29) by Snyder et al (2016). Randomization was performed by computer module and stratified by site and wound area. The primary outcome was the percentage of patients with complete wound closure at 6 weeks. The per protocol population included 11 patients in the AmnioExcel group and 10 in the SOC group. For the ITT population, 33% (95% CI, 25.0% to 46.4%) of patients in the AmnioExcel group achieved wound closure by 6 weeks compared with 0% of the SOC group ($p=0.017$). In the per-protocol analysis, 45.5% of patients treated with AmnioExcel achieved wound closure by 6 weeks compared with 0% in the SOC arm ($p=0.008$) with a 95% CI of the responder ratio of 32.9% to 58.0% ($p=0.014$). Power analysis was not described, and 8 patients withdrew early (4 in each group), raising questions about the reliability of the effect size.

Biovance

Smiehl et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types, including 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers. This study showed the effectiveness of d-HAM in a real-world setting. The size of the wounds at baseline ranged from less than 2 cm² (35.4% of wounds) to over 25 cm² (9.0% of wounds). Ninety-eight percent were on the lower extremities. Twenty-eight ulcers had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex), including 10 diabetic foot wounds. For all wound types, 41.6% closed, with a mean time to closure of 8 weeks and a mean of 2.4 amniotic membrane applications. In the subgroup of 112 patients who practiced good wound care, including offloading or compression therapy as indicated, 49.6% of wounds closed by a mean of 7.4 weeks. Wounds that had not closed during the observation period decreased in size by a mean of 46.6%.

EpiFix vs Standard of Care

Zelen et al (2013) reported on an industry-sponsored, nonblinded, RCT comparing use of EpiFix d-HAM (n=13) with SOC (n=12) for diabetic foot ulcers of at least 4 weeks in duration. EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a compression dressing. The standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix-treated wounds had reduced in size by a mean of 97% compared

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with 32% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wound sizes were reduced by 98.4% with EpiFix treatment compared with -1.8% for SOC. The healing rate was 92% with EpiFix compared with 8% with SOC alone. At the trial conclusion, unhealed wounds from the control group were treated with EpiFix. The mean duration of foot ulcers at the beginning of treatment was 19.4 weeks (range, 6.0-54 weeks) for the combined group. Follow-up was available at 9 to 12 months after primary healing in 18 of 22 eligible patients. Examination of these 18 patients found that 17 (94.4%) wounds remained fully healed. In a subsequent report by Zelen et al (2014), weekly application of EpiFix resulted in significantly faster healing (n=20; mean, 2.4 weeks) compared with biweekly application (n=20; mean, 4.1 weeks; p=0.039). All wounds treated weekly had healed by week 8 compared with 75% of wounds treated biweekly (p=0.047)

EpiFix vs Apligraf

EpiFix d-HAM was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al (2015, 2016). Sixty patients with less than 20% wound reduction during a 2-week run-in period were randomized to treatment with EpiFix, Apligraf, or standard wound care. Although patients and site investigators could not be blinded due to differences in products, wound healing was verified by 3 independent physicians who evaluated photographic images. Median wound size was 2.0 cm² (range, 1.0-9.0 cm²) and median duration of the index ulcer was 11 weeks (range, 5-54 weeks). After 6 weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for SOC; 95% of wounds had healed completely in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care (p=0.003). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix compared with 49 days for both Apligraf and SOC (p<0.001). This study was extended to 12 weeks with 100 patients who were treated with either EpiFix (n=32), Apligraf (n=33), or standard wound care (n=35). Patients whose wound failed to heal by at least 50% by 6 weeks exited the study; this included 4 patients in the Apligraf group and 13 in the SOC group. An additional 5 SOC patients withdrew from the study. Patients treated with EpiFix had a higher probability of wound healing (hazard ratio, 5.66; 95% CI, 3.03 to 10.57; p<0.001) compared with SOC and required fewer weekly treatments (3.4) compared with wounds treated with Apligraf (5.9; p=0.003).

Kirsner et al (2015) reported on an industry-sponsored observational study comparing the effectiveness of Apligraf and EpiFix in a real-world setting. Data were obtained from a wound care-specific database from 3000 wound care facilities. The database included profiles of 1458 diabetic ulcers treated for the first time in 2014 with Apligraf (n=994) or EpiFix (n=464). Using the same criteria as the study by Zelen (2015; described above), data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Selection criteria for foot wounds included size between 1 cm² and 25 cm², duration of 1 year or less, and wound reduction of 20% or less in the 14 days before treatment. Although wounds for the 2 groups were comparable at baseline, the rationale for using a particular product was not reported. One hundred sixty-three wounds were treated with Apligraf (mean, 2.5 applications) and 63 were treated with EpiFix (mean, 3.5 applications, p=0.003). By week 24, 72% of wounds treated with Apligraf and 47% of

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wounds treated with EpiFix had closed ($p=0.01$). Median time to closure was 13.3 weeks for Apligraf and 26.0 weeks for EpiFix ($p=0.01$). This study was found to be at risk of selection bias in determining treatment assignment.

Cryopreserved Placental Membrane

Grafix vs Standard of Care

Grafix cryopreserved placental membrane was compared with standard wound care in a 2014 multicenter RCT. Strengths of this trial included power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Ninety-seven patients with chronic diabetic foot ulcers were randomized to Grafix or standard wound therapy, both administered once a week for up to 12 weeks. Power analysis indicated that 94 patients per arm would be needed. However, after prespecified interim analysis at 50% enrollment, the blinded review committee recommended that the trial be stopped due to the efficacy of the treatment. ITT analysis from the blinded evaluation phase showed a significant increase in the proportion of patients achieving the primary outcome of wound closure by 12 weeks (62.0% vs 21.3%, $p<0.001$) and a decrease in the median time to complete wound closure (42.0 days vs 69.5 days, $p=0.019$). Safety evaluation found that fewer Grafix-treated patients experienced at least 1 adverse event (44.0% vs 66.0%, $p=0.031$) or had wound-related infections (18.0% vs 36.2%, $p=0.044$), with a trend toward fewer hospitalizations related to infections (6% vs 15%, $p=0.15$).

Section Summary: Diabetic Lower-Extremity Ulcers

The evidence on amniotic and placental membrane products for the treatment of diabetic lower-extremity ulcers includes several RCTs comparing HAM with SOC or with an established advanced wound care product. All of these industry-sponsored studies included evaluation of wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the amniotic membrane products evaluated in RCTs (eg, AmnioBand Membrane, EpiFix, Grafix), results indicated improved outcomes compared with SOC, and outcomes that are at least as good as the advanced wound care product Apligraf. Also, a registry study for Biovance showed improved health outcomes, with a magnitude of benefit similar to that observed in the RCTs for other products.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Dehydrated Amniotic Membrane

EpiFix

Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Table 2). The primary outcome in this trial was the proportion of patients with 40% wound closure at 4 weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 3). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the 4 week study. There was no significant difference in healing for wounds given 1 vs 2 applications of amniotic membrane (62% vs 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations

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included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.

A second industry-sponsored multicenter open-label RCT (Bianchi et al, 2017) evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM and compression therapy or compression therapy with standard dressing (see Table 2). Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% CI, 1.25 to 4.10; p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. Healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (see Table 3). There were several limitations of this trial. Nineteen (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix group vs 11% from the control group). Also, the trial did not use ITT analysis. Had all excluded patients been considered treatment failures, the difference between groups would have been 17% (48% wound healing for EpiFix vs 31% for controls). There was also a difference between the groups in how treatment failures at 8 weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at 8 weeks were considered study failures and treated with advanced wound therapies. Although the trialists noted that only 1 patient from this group had healed by weeks 12 and 16, reporting is unclear about how many patients from the d-HAM group would have been considered treatment failures at 8 weeks using the same cutoff.

Table 2. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Serena et al (2014)	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm ² treated for at least 14 d	1 (n=26) or 2 (n=27) applications of EpiFix plus compression (n=53)	Compression therapy alone (n=31)
Bianchi et al (2017)	U.S.	15	2015-2017	128 patients with a full-thickness VLU of at least 30-d duration	Weekly EpiFix plus moist wound therapy plus compression (n=64; 52 analyzed)	Moist wound therapy plus compression (n=64; 57 analyzed)

RCT: randomized controlled trial; VLU: venous leg ulcer.

Table 3. Summary of Key RCT Results

Study	Percent With 40% Wound Closure at 4 Weeks	Percent With Complete Wound Closure at 4 Weeks	Percent With Complete Wound Closure at 12 Weeks	Percent With Complete Wound Closure at 16 Weeks
Serena et al (2014)				
EpiFix	62	11.3		
Control	32	12.9		
p	0.005			
Bianchi et al (2017)				

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EpiFix	60	71
Control	35	44
p	0.013	0.007

RCT: randomized controlled trial.

Biovance

As described above, Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers. Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with SOC is unknown.

Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency

Well-designed and well-conducted RCTs are comparing HAM with SOC for venous lower-extremity ulcers and evaluating the outcome of complete wound closure are needed to demonstrate efficacy. The evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix. The RCT by Serena (2014) reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and SOC. The study by Bianchi (2017) evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, data interpretation is limited by the differential loss to follow-up and exclusions between groups and the lack of ITT analysis. Corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy. The corroborating RCTs should report ITT analysis, with analysis of all patients, including those who were off treatment or had protocol deviations and exclusions. While per protocol analysis can supplement the results, it is not sufficient to determine the effect of the treatment on health outcomes.

OSTEOARTHRITIS

ReNu

A feasibility study (N=6) of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis was reported in 2016. A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. An RCT is in progress.

Section Summary: Osteoarthritis

Current evidence is insufficient to support definitive conclusions on the utility of c-HAM in the treatment of knee osteoarthritis.

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PLANTAR FASCIITIS

One systematic review and 2 randomized pilot studies were identified on the treatment of plantar fasciitis using an injection of micronized HAM.

Systematic Review

A 2016 network meta-analysis of 22 RCTs (total N=1216 patients) compared injection therapies for plantar fasciitis. In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. The minimum clinically important difference was defined as -9 mm on a visual analog scale, which is substantially lower than the 30% (20-mm) decrease in visual analog scale score for pain more typically used. Secondary outcomes included total and subscores for the Foot Health Status Questionnaire (FHSQ), with a minimum clinically important difference defined as 7 on the FHSQ function and 9 on the FHSQ general foot health subscales. Overall, the risk of bias was low for randomization and blinding of participants, high for blinding of personnel, and uncertain for allocation concealment and outcome reporting. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term. However, this finding was based only on a single RCT. When the efficacy of d-HAM was compared with corticosteroid injections, the mean difference in visual analog scale score was a modest at -7.32 out of 100 (95% CI, -11.2 to -3.38) and the mean difference in the FHSQ score was 31.2 (95% CI, 13.9 to 48.6). Outcomes at 2 to 6 months (7 RCTs) favored botulinum toxin for pain and PRP for composite outcomes.

Clarix Flo

One small (N=23), industry-sponsored, double-blind trial (2015) found similar improvements with an injection of c-HAM (Clarix Flo) and corticosteroid injection. Another industry-sponsored, patient-blinded study by Zelen et al (2013; N=45) compared injection of saline with d-HAM (AmnioFix) 0.5 mL or 1.25 mL in patients who had symptoms recalcitrant to conservative treatment. In the 2 d-HAM groups, scores on the American Orthopaedic Foot and Ankle Society hindfoot scale improved by about 50 points over 8 weeks compared with 10 points for controls ($p<0.001$). FACES pain scores decreased from 8.7 out of 10 at baseline to 0.8 at 8 weeks with d-HAM, compared with a decrease from 8.0 to 4.6 for controls ($p<0.001$).

Section Summary: Plantar Fasciitis

The evidence on injection of particulated amniotic membrane and amniotic fluid for the treatment of plantar fasciitis is limited. Evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of 2 different doses of d-HAM with saline. Power analyses were not reported. A network meta-analysis, which identified only the Zelen et al trial, concluded that d-HAM was more effective than corticosteroid. However, these 2 small trials did not provide sufficient evidence to demonstrate an improvement in health outcomes for this common condition. Additional study in a larger number of patients is needed to demonstrate consistency in results.

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SUTURED HAM GRAFT FOR OPHTHALMOLOGIC CONDITIONS

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

Neurotrophic Keratitis

Khokhar et al (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens. At the 3-month follow-up, 11 (73%) of 15 patients in the HAM group showed complete epithelialization compared with 10 (67%) of 15 patients in the conventional group. This difference was not significantly significant.

Following Pterygium Repair

A number of RCTs have been reported on the use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified 4 RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total N=1866 patients) arrived at the same conclusion.

Stevens-Johnson Syndrome

One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone. The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of Stevens-Johnson syndrome resulted in improved visual acuity (p=0.042), better tear breakup time (p=0.015), improved Schirmer test results (p<0.001), and less conjunctival congestion (p=0.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=0.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=0.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

Persistent Epithelial Defects and Ulceration

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease. They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis.

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Ocular Burns

A 2012 Cochrane review evaluated the evidence on HAM graft for acute ocular burns. Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to c-HAM plus medical therapy or medical therapy alone. In the subset of 36 patients with moderate ocular burns treated within 7 days, 13 (65.0%) of 20 control eyes and 14 (87.5%) of 16 eyes treated with amniotic membrane transplantation had complete epithelialization by 21 days. There was a trend ($p=0.09$) toward a reduced relative risk of failure of epithelialization in the treatment group. Mean logarithm of the minimum angle of resolution (logMAR) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1 (5.9%) of 17 eyes treated with amniotic membrane transplantation and 1 (6.7%) of 15 control eyes were epithelialized by day 21. There was no significant difference in final visual acuity (1.77 logMAR in eyes treated with amniotic membrane transplantation vs 1.64 in control eyes; $p=0.79$). The risk of bias was considered high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. Reviewers determined that conclusive evidence supporting the treatment of acute ocular surface burns with amniotic membrane transplantation was lacking.

Bullous Keratopathy

Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation. Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy. Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

Dry Eye Syndrome, Corneal Perforation, and Limbus Stem Cell Deficiency

No RCTs were identified on these other ophthalmic indications.

Section Summary: Sutured HAM Graft for Ophthalmic Conditions

The most widely studied condition with a technology assessment evaluating RCT evidence is the use of HAM following pterygium repair. The assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT on HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to those for conventional therapy. One RCT has shown that application of c-HAM in the early stages of Stevens-Johnson syndrome leads to clinically significant improvement compared with medical therapy alone. A 2012 Cochrane review found an RCT evaluating HAM graft for acute ocular burns. The trial suggested a benefit for HAM in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and lack of masking to treatment condition. A trial on HAM for the treatment of bullous keratopathy reported that there was no

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difference in clinical outcomes between HAM and stromal puncture. Other indications have been studied only in case series.

HAM WITHOUT SUTURE FOR OPHTHALMIC CONDITIONS

Traditionally, amniotic membrane has been fixed onto the eye with sutures or glue or placed under a bandage contact lens for a variety of ocular surface disorders. Several devices have been reported that use a ring around a c-HAM allograft that allows it to be inserted under topical anesthesia similar to insertion of a contact lens. The easier insertion may lead to more widespread use, such as dry eye disease and for healing after photorefractive keratectomy (PRK). The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

Dry Eye Disease

John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment. The c-HAM was applied for an average of 3.4 days (range, 3-5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both 1-month and 3-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at 3 months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The Prokera c-HAM device was also evaluated in a series by Cheng et al (2016). The senior author of the study holds the patent on Prokera. This retrospective review assessed 10 patients treated with the self-retained device for moderate-to-severe dry eye disease. In this study, these 10 patients had moderate-to-severe dry eye syndrome despite conventional medical treatment. The c-HAM device was placed in 15 eyes (1 eye at a time) for a mean of 4.9 days (range, 2-8 days), after which the c-HAM was either dissolved or cloudy. Treatment resulted in symptomatic relief for a mean of 4.2 months (range, 0.3-6.8 months) after a single treatment. Symptomatic improvement was accompanied by statistically significant reductions of Ocular Surface Disease Index scores, use of topical medications, conjunctival hyperemia, corneal staining (all $p < 0.001$), and a trend toward improved visual acuity ($p = 0.06$).

Photorefractive Keratectomy

Vlasov et al (2016) reported on a prospective, nonrandomized controlled trial evaluating the effect of sutureless amniotic membrane (Prokera) on corneal wound healing after PRK. Forty patients (80 eyes) had PRK for myopia. After surgery, a high-oxygen-transmissible bandage contact lens was applied on the dominant eye and cryopreserved amniotic membrane on the nondominant eye. Patients were assessed daily until complete corneal re-epithelialization occurred in both eyes and then at 2 weeks and 1, 3, 6, and 12 months after that. The primary outcome was re-epithelialization, which was assessed daily with slit lamp

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examination, fluorescein staining, and photography. The time to complete reepithelization was faster in eyes treated with a bandage contact lens (3.7 days; range, 3-7 days) than with the amniotic membrane product (4.6 days; range, 3-16 days). Initially, patients reported greater discomfort and dryness with amniotic membrane. Visual and clarity and optical quality of the cornea were similar in the eyes treated with the amniotic membrane graft and bandage contact lens.

Other Indications

Use of Prokera has also been reported for refractory ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency.

Section Summary: HAM Without Suture for Ophthalmic Conditions

Current evidence on the use of the Prokera device includes an RCT with 20 patients, a within-subject comparative study, and case series. The RCT with 20 patients found a benefit of Prokera in patients with dry eye disease, but the prospective comparative trial identified found no benefit of HAM compared with a bandage contact lens when used for wound healing after PRK. While the studies reported generally positive effects, high-quality RCTs are needed to determine the effect of sutureless self-contained HAM on corneal healing.

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 (ie, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes 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 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 analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, 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 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of lower-extremity venous ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure did not differ between EpiFix and

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standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the standard of care for venous insufficiency ulcers are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Osteoarthritis

For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. 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 the effects of the technology on health outcomes.

Plantar Fasciitis

For individuals who have plantar fasciitis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Research on HAM injections for plantar fasciitis is at an early stage. The evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of HAM and amniotic fluid injections on plantar fasciitis pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ophthalmic Conditions

For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes several RCTs and a technology assessment. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The most widely studied condition with a technology assessment of RCT evidence is the use of HAM following pterygium repair. The technology assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT evaluating HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to conventional therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes a systemic review article and RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A 2012 Cochrane review found a single RCT on HAM graft for acute ocular burns. The trial suggested a benefit in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and the lack of masking of the treatment condition. A trial assessing HAM for the treatment of bullous keratopathy reported no difference in

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clinical outcomes between HAM and stromal puncture. RCTs are needed to evaluate the benefit of HAM for these indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic conditions who receive HAM without suture, the evidence includes an RCT (N=20), a within-subject comparative study, and case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Traditionally, amniotic membrane has been sutured onto the eye for a variety of severe ocular surface disorders. The Prokera device is novel because it has a ring around the cryopreserved HAM allograft that permits it to be inserted under topical anesthesia, similar to insertion of a contact lens, allowing for more widespread use. Use of Prokera has been reported for refractory dry eye syndrome, ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency. Current evidence on its use is limited. While the small RCT and case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared with a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs are needed to determine whether sutureless HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 08/19/2015

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Louisiana

Amniotic Membrane and Amniotic Fluid

Policy # 00458
 Original Effective Date: 08/19/2015
 Current Effective Date: 05/16/2018

Current Effective Date: 05/16/2018

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.

Next Scheduled Review Date: 08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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, 65778, 65779, 96372
HCPCS	Q4100, Q4131, 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, V2790 New codes added 1/1/18: Q4177, Q4178, Q4179, Q4181

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ICD-10 Diagnosis	All related diagnoses
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*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. 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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