Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 08/23/2017

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 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 human amniotic membrane 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 human amniotic membrane 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 human amniotic membrane 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 human amniotic membrane for all indications 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 membrane products and indications not listed above to be investigational.*

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 (see Table 1).

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. 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, lubrican, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.

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

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryopreserved,</td>
<td>Amnion</td>
</tr>
<tr>
<td></td>
<td>Dehydrated, or</td>
<td>(C)</td>
</tr>
<tr>
<td></td>
<td>Extracted</td>
<td></td>
</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>AmbioDry® (IOP Ophthalmics)</td>
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</tr>
<tr>
<td>AmnioBand® Membrane (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioClear™ (Liventa Bioscience)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmnioExcel® (Derma Sciences)</td>
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<tr>
<td>AmnioFix® (MiMedx)</td>
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<tr>
<td>AmnioGraft® (Bio-Tissue)</td>
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<td>Artacent® Wound (Tides Medical)</td>
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<tr>
<td>BioDDryFlex® (BioD)</td>
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<td>BioDefence™ (BioD)</td>
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<tr>
<td>BioSkin (thin - 45 microns, HRT)</td>
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<td>X</td>
</tr>
<tr>
<td>BioSkin (thick - 200 microns, HRT)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Biovance® (Alliqua Biomedical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Clarix® (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Cygnus (Vivex Biomedical)</td>
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</tr>
<tr>
<td>Cygnus Max (Vivex Biomedical)</td>
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<tr>
<td>EpiCord™ (MiMedx)</td>
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<tr>
<td>EpiFix® (MiMedx)</td>
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<tr>
<td>Dermavest™ (Aedicell)</td>
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<td>X</td>
</tr>
<tr>
<td>Grafix® (Osiris)</td>
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</tr>
<tr>
<td>Guardian/AmnioBand® (MTF Wound Care)</td>
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</tr>
<tr>
<td>Neo® 100 (Amnio Medical)</td>
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<td>X</td>
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<tr>
<td>Neo® Cord (Amnio Medical)</td>
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<td>X</td>
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<tr>
<td>Neo® Wound Allograft (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>NuShield™ (NuTech Medical)</td>
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</tr>
<tr>
<td>PalinGen® Membrane (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Plurivest™ (Aedicell)</td>
<td>C</td>
<td>X</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokera® (Bio-Tissue)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Revitalon™ (Medline Industries)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® (45 microns, Skye Biologics)*</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® (200 microns, Skye Biologics)*</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td><strong>Suspension, particulate, or extraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmnioBand® Particulate (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioMatrix® (Derma Sciences)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioVisc™ (Lattice Biologics)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>BioSkin® Flow (HRT) b</td>
<td>E</td>
<td>X</td>
</tr>
<tr>
<td>Clarix® Flo (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Interfyl™ (Alliqua Biomedical)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Flo (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>OrthoFlo™ (MiMedx)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
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<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® Flow (Skye Biologics) b</td>
<td>E</td>
<td>X</td>
</tr>
</tbody>
</table>

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

* Processed by HRT and marketed by under different tradenames.

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

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
For conditions in which subjective measures are the primary outcomes, randomized controlled trials (RCTs) are particularly important due to the expected placebo effect and variable natural history. RCTs are also important because there may be numerous confounders of outcomes, and nonrandomized comparisons are prone to selection bias. For these reasons, RCTs are essential to demonstrate the clinical effectiveness of amniotic membrane and amniotic membrane injections compared with alternatives such as continued medical management or other established treatments. Therefore, the products assessed in this review are those that have RCT evidence. For indications where treatment with some amniotic membrane products has been established, nonrandomized studies that include patients with similar characteristics and have similar magnitude of benefit may be considered sufficient evidence.

The primary end points of interest for trials of wound closure are as follows, consistent with guidance from the U.S. FDA for industry in developing products for 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 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 study was adequately powered to detect a difference of 45% between groups in the primary outcome (the proportion of wounds 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 to 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 study 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 Care
AmnioExcel dehydrated human amniotic membrane (d-HAM) was compared with standard care 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 to 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 to 0% in the SOC arm (p=0.008) with a 95% confidence interval 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 Registry**

In 2015, Smiell et al 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 cm$^2$ (35.4% of wounds) to over 25 cm$^2$ (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 Care**

In 2013, Zelen et al reported 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. 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 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 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.

**EpiFix vs Apligraf**

EpiFix d-HAM was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al (2015). Sixty patients 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 cm$^2$ (range, 1.0-9.0 cm$^2$) and median duration of the index ulcer was 11 weeks (range, 5-54 weeks).
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 \(p<0.001\).

In 2015, Kirsner et al reported 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 1458 diabetic ulcers treated for the first time in 2014 with Apligraf \(n=994\) or EpiFix \(n=464\). Using the same criteria as the 2015 study by Zelen (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 \(cm^2\) and 25 \(cm^2\), duration of 1 year or less, and wound reduction of 20% or less in the 14 days prior to 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 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 is at risk of selection bias in determining treatment assignment.

**Cryopreserved Placental Membrane**

**Grafix vs Standard 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 to 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 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 compared HAM to SOC or to 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 to SOC, and outcomes that are at least as good as the advanced
wound care product Apligraf. In addition, 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**

In 2014, Serena et al reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy to compression therapy alone for venous leg ulcers. Ulcers were included if they were chronic (>1 month in duration); extended through the full thickness of the skin but not down to muscle, tendon, or bone; and had been treated with compression therapy for at least 14 days. Eighty-four participants were enrolled and assigned to a single EpiFix allograft (n=26), 2 allografts (n=27), or compression therapy alone (n=31). The primary outcome (proportion of patients with 40% wound closure at 4 weeks) was achieved by 62% in the combined EpiFix groups and by 32% in the control group (p=0.005). During the 4-week trial period, 6 (11.3%) patients in the combined EpiFix group and 4 (12.9%) in the control group achieved complete wound closure. Secondary outcomes, which evaluated the use of 1 versus 2 applications of amniotic membrane, showed no significant difference in outcomes (62% vs 63%). Strengths of this study included adequate power and ITT analysis with last observation carried forward. Limitations 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.

**Biovance**

As described above, in 2015, Smiell et al 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**

Given the lack of difference between 1 and 2 applications of EpiFix and the lack of difference between the experimental and control groups in complete wound closure at 4 weeks, and because no HAM products have been shown to improve healing of venous ulcers in comparative trials, additional study is needed to evaluate the effect of this treatment on health outcomes.

**OSTEOARTHRITIS**

**ReNu**

A feasibility study (N=6) of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid–derived cells (ReNu) for the treatment of knee osteoarthritis was reported in 2016. A single intra-
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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 effects, aside from a transient increase in pain, were noted. An RCT is in progress.

PLANTAR FASCIITIS
One systematic review and 2 randomized pilot studies were identified on the treatment of plantar fasciitis using 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 (PRP), 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 (MCID) was defined as -9 mm on a visual analog scale (VAS), which is substantially lower than the 30% or 20-mm decrease in VAS score for pain more typically used. Secondary outcomes included total and subscores for the Foot Health Status Questionnaire (FHSQ), with an MCID defined as 7 on the FHSQ function and 9 on the FHSQ general foot health subscales. Overall, 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 found d-HAM had the highest probability for improvement in pain and composite outcomes in the short term. However, this finding was based only on 1 RCT. When the efficacy of d-HAM was compared to corticosteroid injections, the mean difference in VAS 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 study (2015) found similar improvements with injection of c-HAM (Clarix Flo) compared with corticosteroid injection. Another industry-sponsored, patient-blinded study (2013) by Zelen et al (N=45) compared injection of saline to d-HAM (AmnioFix) 0.5 mL or 1.25 mL in patients with 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 the 8 weeks of the study 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). Longer follow-up is ongoing.

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 are not sufficient 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.

SUTURED HAM GRAFT FOR OPHTHALMOLOGIC CONDITIONS
Sutured HAM graft has been evaluated for a variety of ophthalmologic conditions.

Neurotrophic Keratitis
In 2005, Khokhar and Natung reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or to conventional treatment with tarsorrhaphy or bandage contact lens. At the 3-month follow-up, 11 (73.3%) of 15 patients in the HAM group showed complete epithelialization compared to 10 (66.7%) of 15 in the conventional group. This difference was not significantly significant.

Following Pterygium Repair
A number of RCTs have been reported on 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.

Stevens-Johnson Syndrome
One RCT from India (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or to 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), tear breakup time (p=0.015), 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 compared dramatically with the medical therapy alone group, which had 11 (44%) of 25 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
In 2004, Bouchard and John wrote a review 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 rarity of the diseases and the absence of a 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.

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 to 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 AMT-treated eyes had complete epithelialization by 21 days. There was a trend (p=0.09) toward a reduced relative risk of failure of epithelization 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 AMT-treated eyes and 1 (6.7%) of 15 control eyes were epithelialized by day 21. There was no significant difference in final visual acuity, which was 1.77 logMAR in the treated eyes and 1.64 in the control group (p=NS). 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 AMT is lacking.

Bullous Keratopathy
Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation. In 2013, Dos Santos Paris et al published an RCT that compared fresh HAM to 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 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 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 to medical therapy alone. A 2012 Cochrane review found 1 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
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treatment condition. A trial on HAM for the treatment of bullous keratopathy reported that there was no 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).

Dry Eye Disease
The Prokera c-HAM device was evaluated in a 2016 series by Cheng et al. The senior author of the study (S.C.G. Tseng) 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 to 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
In 2016, Vlasov et al 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 thereafter. The primary outcome was re-epithelialization, which was assessed daily with slitlamp examination, fluorescein staining, and photography. The time to complete reepithelialization 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 between the amniotic membrane graft eyes and bandage contact lens eyes.

Other
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 (referenced in Cheng et al, 2016).
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Section Summary: HAM Without Suture for Ophthalmic Conditions

Current evidence on use of the Prokera device includes 1 within-subject comparative study and case series. While the case series reported generally positive effects, RCTs are needed to determine the effect of sutureless self-contained HAM on corneal healing. The single prospective comparative trial identified found no benefit of HAM compared to a bandage contact lens when used for wound healing after PRK. RCTs are needed to determine whether HAM improves healing for these various disorders.

SUMMARY OF EVIDENCE

Diabetic Lower-Extremity Ulcers
For individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of human amniotic membrane (HAM; 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 to standard care or to 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 (AmnioBand Membrane, Biovance, Epifix, Grafix), results have shown improved outcomes compared to 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 patch or flowable formulation of HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. In a randomized comparison of a cryopreserved HAM product to standard of care, there was no difference between the experimental and controls groups in complete wound closure at 4 weeks. Because HAM has not been shown to improve healing of venous ulcers in controlled studies, comparative studies on other HAM products 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 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 was for a precursor to a larger RCT of HAM injection. Additional trials, which will have a larger sample sizes 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.

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Plantar Fasciitis
For individuals who have plantar fasciitis who receive 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 2 RCTs and a systematic review that included 1 RCT. 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 clinical outcomes between HAM and stromal puncture. RCTs are needed to evaluate the benefit of HAM for these other 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 1 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 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 use of the Prokera device is limited. While the case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens for
healing a wound after photorefractive keratectomy. RCTs are needed to determine whether HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

A review of the literature has shown that amniotic membrane has been used for nearly 2 decades for ophthalmic disorders, although RCT evidence is limited. Therefore, clinical input was requested on the specific disorders for which amniotic membrane would be expected to improve health outcomes and use is consistent with generally accepted medical practice. Input supported the use of sutured or glued amniotic membrane for neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Those providing input had low confidence that sutureless amniotic membrane performed as well or better than sutured amniotic membrane.

**CLINICAL INPUT**

**OBJECTIVE**

In 2017, clinical input was sought to help determine the appropriate use in clinical practice of human amniotic membrane (also referred to as amniotic membrane graft [AMG]) for ophthalmic disorders.

**RESPONDENTS**

Clinical input was provided on behalf of the American Academy of Ophthalmology (AAO) by Dr. David Glasser, Chair of AAO’s Health Policy Committee.

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by the specialty society is attributed to the individual physician and is not a statement from the specialty society. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a special society and/or physician member designated by the specialty society or clinical health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.
With regard to the use of AMG in each of the following ophthalmic disorders:

<table>
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<th>Clinical Indication</th>
<th>Respondent</th>
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<td>Neurotrophic keratitis</td>
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<tr>
<td>Corneal ulcers and melts</td>
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<td>Corneal perforation</td>
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<td>Bullous keratopathy</td>
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<td>Limbal stem cell deficiency</td>
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<td>Stevens Johnson</td>
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<td>Persistent epithelial defects</td>
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<td>Severe dry eye</td>
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Confidence Level that Evidence Supports Improved Health Outcomes

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Confidence Level that Clinical Use is in Accordance with Generally Accepted Medical Practice

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Additional Comments

With regard to the 9 indications listed above, there was lower range confidence that there is adequate evidence demonstrating that sutureless fixation HAM (also called AMG) (eg, Prokera, AmbioDisk) performs as well as or better than sutured or glued AMG.

Use of AMG would be expected to improve health outcomes and is considered consistent with generally accepted medical practice for:

1. “patients with an epithelial defect that (1) has failed to completely close after 5 days of conservative treatment (2) 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 AMG. AMG requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day.”

2. “We are in agreement that larger controlled studies are needed to show benefit of AMG in dry eye disease, where the disease is common and such studies should be easy to perform.”

References
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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.

Next Scheduled Review Date: 08/2018

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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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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.

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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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