LOUISIANA BLUE

Amniotic Membrane and Amniotic Fluid

Policy # 00458
Original Effective Date: 08/19/2015
Current Effective Date: 07/01/2025

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

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

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

When Services Are Eligible for Coverage

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

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

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

- Initial treatment may be approved for up to 4 applications over 6 weeks period per nonhealing wound that is not infected and patient agrees to comply with adequate mechanical offloading (see Policy Guidelines); or
- Additional applications after initial 6 weeks may be eligible for coverage when the following criteria are met:
    - Documented objective evidence of wound healing (e.g. development and presence of healthy granulation tissue with progressive wound contracture or decreasing depth); and
    - Approved HAM product is applied no more frequently than in one-week intervals; and
    - Patient remains compliant with adequate mechanical offloading; and
    - Continued treatment may be approved for up to 4 additional applications over 6 more weeks, per wound treated.

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

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

© 2025 Louisiana Blue

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

When Services Are Considered Investigational

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

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

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

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

Based on review of available data, the Company considers all other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, Wharton's jelly, and products noted in Table PG2 in Policy Guidelines) not listed above to be **investigational.***

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

- Treatment of lower-extremity ulcers due to venous insufficiency
- Repair following Mohs micrographic surgery

- When criteria above are not met including using more than 8 applications beyond 12 weeks for diabetic foot ulcers

Policy Guidelines

Non-healing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks, based on the entry criteria for clinical trials (eg, Zelen et al [2015]).

Tables PG1 and PG2 list the medically necessary and investigational amniotic products that have an HCPCS code.

Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022]).

This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code.

Table PG1 Amniotic Products Listed in the Policy Statements

Trade Name	Supplier	HCPCS Code
Affinity®‡	Organogenesis (previously NuTech Medical)	Q4159
AmnioBand®‡ Membrane	MTF Wound Care	Q4151
AmbioDisk	Katena	V2790
AmnioExcel®‡	Integra	Q4137
AmnioGraft	Bio-Tissue	V2790
Artacent Ocular	Tides medical	V2790
Biovance®‡	Celularity	Q4154
Epicord®‡	MiMedx	Q4187
Epifix®‡	MiMedx	Q4186
Grafix®‡	Osiris	Q4132, Q4133
NuShield®‡	Organogenesis	Q4160
Prokera	Bio-Tissue	V2790
Vendaje Optic	BioStem Technologies	V2790

Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane	Amnio Technology	Q4355

Abiomend Membrane and Abiomend Hydromembrane	Amnio Technology	Q4356
ACApatch™‡	RegenTX Partners	Q4325
Acesso	Dynamic Medical Services	Q4311
Acesso ac	Dynamic Medical Services	Q4312
Acesso dl	Dynamic Medical Services	Q4293
Acesso tl	Dynamic Medical Services	Q4300
Activate matrix	Nvision Biomedical Technologies	Q4301
Advograft one	RMBB Health	Q4380
Advograft dual	RMBB Health	Q4382
Aeroguard	C5 Biomedical	Q4370
alloPLY™‡	RegenTX Partners	Q4323
Allogen	Vivex Biologics	Q4212
AlloWrap™‡	AlloSource	Q4150
AmchoPlast®‡	RMBB Health	Q4316
Amchoplast excel	Cellution Biologics	Q4372
AmchoPlast FD™	LifeCell International Pvt Ltd.	Q4360
AmchoThick™	Cellution Biologics	Q4368
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™‡	Bone Bank Allografts	Q4188
AmnioBand®‡ Particulate	MTF Wound Care	Q4168
AmnioExcel®‡	Intergra Lifesciences	Q4137
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amnioplast 1	LifeCell International	Q4334
Amnioplast 2	LifeCell International	Q4335
AmnioPlast 3™	Cellution Biologics	Q4369
Amniotext	Regenerative Labs	Q4245
AmnioTX™‡	RegenTX Partners	Q4324
Amnio tri-core amniotic	Stability Biologics	Q4295
Amnio quad-core	Stability Biologics	Q4294
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™‡	Stability Biologics	Q4227
Amniocore pro	Stability Biologics	Q4298
Amnicore pro+	Stability Biologics	Q4299
AmnioCore SL	Stability Biologics.	Q4367
Amniodefend ft matrix	Sequence LifeScience	Q4379
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix®‡	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235

Amniotext patch	Regenerative Labs	Q4247
AmnioWrap2™‡	Biostem Technologies	Q4221
Amnio Burgeon Membrane and Hydromembrane	One BioTech LLC.	Q4363
Amnio Burgeon XPlus Membrane and XPlus Hydromembrane	One BioTech LLC.	Q4364
Amnio Burgeon Dual-Layer Membrane	One BioTech LLC.	Q4365
ArdeoGraft	Surgenex	Q4333
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent®‡ Wound	Tides Medical	Q4169
Artacent c	Tides Medical	Q4336
Artacent®‡ Cord	Tides Medical	Q4126
Artacent trident	Tides Medical	Q4337
Artacent velos	Tides Medical	Q4338
Artacent vericlen	Tides Medical	Q4339
Ascent	StimLabs	Q4213
Axolotl Graft™‡	Axolotl Biologix	Q4331
Axolotl DualGraft™‡	Axolotl Biologix	Q4332
Axolotl ambien or Axolotl Cryo	Axolotl Biologix	Q4215
BioDDryFlex®‡	BioD	Q4138
BioDfence™‡	Integra Life Science	Q4140
BioWound, BioWound Plus™‡, BioWound XPlus™‡	Skye Biologics	Q4217
CaregraFT™‡	RegenTX Partners	Q4322
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
ChoriPly	International Tissue Inc.	Q4359
Clarix®‡	Amniox Medical	Q4156
Clarix®‡ Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Complete aa	Samaritan Biologics	Q4303
Complete aca	Legacy Medical	Q4302
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P or Theracor P or Allacor P	StimLabs	A2035
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170

CYGNUS Disk	VIVEX Biologics (Vivex)	Q4362
Dermacyte	Merakris Therapeutics	Q4248
Dermacyte®‡ AC Matrix	Merakris Therapeutics	Q4343
Dermabind ch	Health Tec Wound Care	Q4288
Dermabind dl	Health Tec Wound Care	Q4287
DermaBind FM™‡	Health Tec Wound Care	Q4313
Dermavest™‡ or Plurivest	AediCell[a]	Q4153
Dual Layer Amnio Burgeon X-Membrane	One BioTech LLC.	Q4366
DuoAmnion™‡	Samaritan Biologics	Q4327
Duograft aa	RegenTX Partners	Q4376
Duograft ac	RegenTX Partners	Q4375
E-Graft™‡	Skye Biologics	Q4318
Emerge matrix	Sequence Life Science	Q4297
Enclose tl matrix	Sequence LifeScience	Q4351
Epifix Injectable	MiMedx	Q4145
EPIXPRESS	MiMedx Group, Inc.	Q4361
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Grafix plus	Smith & Nephew	Q4304
Interfyl®‡	Celularity	Q4171
Lamellas	Keyport Management	Q4292
Lamellas xt	Keyport Management	Q4291
Mantle dl matrix	Sequence LifeScience	Q4349
Matrion	LifeNet Health	Q4201
Matrix HD Allograft Dermis	Royal Wound-X, Inc	Q4345
Membrane wrap-hydro	BioLab Sciences	Q4290
Membrane wrap-lite	BioLab Holdings	Q4373
MOST™‡	Samaritan Biologics	Q4328
Neoguard	C5 Biomedical	Q4371
Neopatch or Therion	CryoLife	Q4176
Neox®‡ Cord	Amniox Medical	Q4148
Neox®‡ Flo	Amniox Medical	Q4155
Neox®‡ Wound	Amniox Medical	Q4156
Novachor	Organogenisis	Q4194
Novafix®‡	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuDYN®‡ DL MESH	Fida Pharma USA	Q4285
NuDYN®‡ SLW	Fida Pharma USA	Q4286
Overlay sl matrix	Sequence LifeScience	Q4352
PalinGen®‡ Dual-Layer Membrane	Amnio Technology	Q4354
PalinGen®‡ Membrane	Amnio Technology	Q4173

PalinGen®‡ SportFlow	Amnio Technology	Q4174
Palisade dm matrix	Sequence LifeScience	Q4350
PelloGraft	Surgenex	Q4320
Plurivest™‡	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Extremity Care	Q4310
Rampart dl matrix	Sequence LifeScience	Q4347
Rebound matrix	Sequence LifeScience	Q4296
Reeva FT	Legacy Medical	Q4314
Regenelink	LifeLink Foundation	Q4315
Reguard	New Life Medical	Q4255
Renew ft matrix	Sequence LifeScience	Q4378
RenoGraft	Surgenex	Q4321
Restorigin	Parametrics Medical	Q4191
Restorigin Injectable	Parametrics Medical	Q4192
Revita	StimLabs	Q4180
Revitalon™‡	Medline Industries	Q4157
Revoshield + amniotic barrier	Revogen Biologics	Q4289
SanoGraft	Surgenex	Q4319
Shelter dm matrix	Sequence LifeScience	Q4346
Sentry sl matrix	Sequence LifeScience	Q4348
SimpliGraft	Xtant Medical	Q4340
Simplimax	Xtant Medical	Q4341
Singlay™‡	Samaritan Biologics	Q4329
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT™‡	Synergy Biologics	Q4183
TheraMend	Lux Therapeutics	Q4342
Trigraft ft	RegenTX Partners	Q4377
Tri-Membrane Wrap™‡	BioLab	Q4344
TOTAL™‡	Samaritan Biologics	Q4330
Vendaje ac	BioStem Technologies	Q4279
VitoGraft	Surgenex	Q4317
WoundEx®‡	Skye Biologics	Q4163
WoundEx®‡ Flow	Skye Biologics	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	Skye Biologics	Q4217
WoundPlus™‡	Skye Biologics	Q4326
Xceed tl matrix	RMBB Health	Q4353
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204
XWRAP Plus®‡	Applied Biologics, LLC.	Q4357
XWRAP Dual®‡	Applied Biologics, LLC.	Q4358

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

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)
Step 1:

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

Step 2:
If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

Dry eye severity level DEWS 3 to 4
Discomfort, severity, and frequency - Severe frequent or constant
Visual symptoms - chronic and/or constant, limiting to disabling
Conjunctival Injection - +/- or +/+
Conjunctive Staining - moderate to marked
Corneal Staining - marked central or severe punctate erosions
Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris
Lid/meibomian glands - Frequent
Tear film breakup time - < 5
Schirmer score (mm/5 min) - < 5

Background/Overview

Human Amniotic Membrane

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

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

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products

that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures. Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

Amniotic Fluid
Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea. The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid-derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In 2024, the U.S. Food and Drug Administration (FDA) issued a public safety notification on amniotic fluid eyedrops. The notice was to inform the public and health care practitioners "that manufacturers are marketing and distributing amniotic fluid eyedrops to treat, mitigate, or cure diseases or conditions such as dry eye disease without the required premarket review and approval, raising potential significant safety concerns." A list of related warning letters issued by the FDA can be found on the FDA website's Warning Letters page using the search term "amniotic fluid."

On December 19, 2024, the FDA issued a warning letter to Integra LifeSciences Corporation stating: "FDA investigators and a microbiologist determined that the above firms manufacture a variety of neurological and neurosurgical devices, including but not limited to, cranial perforators, disposable cottonoid patties and strips as well as collagen based medical devices, that are used for wound care, soft tissue repair and reconstruction surgery. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body."

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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

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

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a. Is for autologous use;
        b. Is for allogeneic use in a first-degree or second-degree blood relative; or
        c. Is for reproductive use."

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

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

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

In 2003, Prokera was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104; product code: NQB). The FDA determined that this device was substantially equivalent to the Symblepharon Ring. The

Prokera device is intended "for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred." The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

Rationale/Source

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

Several commercially available forms of human amniotic membrane (HAM) and amniotic fluid can be administered by patches, topical application, or injection. Amniotic membrane and amniotic fluid are being evaluated for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions.

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch formulation of HAM or placental membrane (ie, Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix, NuShield), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (ie, Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix, NuShield), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Lower-Extremity Ulcers due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch formulation of HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix and 1 multicenter RCT with Amnioband. One RCT 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 the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of

EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. A third RCT demonstrated significantly greater blinded assessor-confirmed rates of complete wound closure at 12 weeks after weekly or twice-weekly application of AmnioBand Membrane with compression bandaging compared with compression bandaging alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Osteoarthritis
For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pilot study assessed the feasibility of a larger RCT evaluating HAM injection. Additional trials, which will have a larger sample size and longer follow-up, are needed to permit conclusions on the effect of this treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Plantar Fasciitis
For individuals who have plantar fasciitis who receive an injection of amniotic membrane, the evidence includes preliminary studies and a larger (N=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in the visual analog score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an interim report with 12-month results pending. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ophthalmic Conditions
Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy
For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Corneal Ulcers and Melts That Do Not Respond to Initial Medical Therapy
For individuals who have corneal ulcers and melts, that do not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-randomized comparative study. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional

RCTs are not expected. The systematic review showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative evidence was identified for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Bullous Keratopathy as a Palliative Measure in Patients Who are Not Candidates for a Curative Treatment (eg, Endothelial or Penetrating Keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Moderate or Severe Stevens-Johnson Syndrome

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

Persistent Epithelial Defects and Ulceration That Do Not Respond to Conservative Therapy
For individuals who have persistent epithelial defects that do not respond to conservative therapy who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on persistent epithelial defects and ulceration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Severe Dry Eye with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy
For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns
For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is Not Immediately Available
For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The standard treatment for corneal perforation is corneal transplantation, however, HAM may provide temporary coverage of the severe defect when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Repair Following Mohs Micrographic Surgery
For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amnionic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of patients requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (p<.0001). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

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

2019 Input
Clinical input was sought to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

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

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) as an alternative to stromal puncture.

- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Persistent epithelial defects and ulcerations that do not respond to conservative therapy.
- Severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.
- Moderate or severe acute ocular chemical burn.
- Corneal perforation when corneal tissue is not immediately available.
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

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

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

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

Step 1:
- Education regarding the condition, its management, treatment, and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

Wound Healing Society
In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment. The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, “healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.” References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

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

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

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06600724a	A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Evaluating PURION Processed Lyophilized Human Amnion/Chorion Membrane (ppLHACM) and Standard of Care Versus Standard of Care Alone in the Treatment of Nonhealing Diabetic Foot Ulcers	170	Aug 2026
NCT04457752[a]	A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®‡) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers	124	Mar 2023
NCT03390920[a]	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jan 2030
NCT04553432[a]	Dry Eye OmniLenz Application of Omnigen Research Study	79 (actual)	Jul 2023
NCT04636229[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	474	Jun 2025
NCT06000410[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	474	Mar 2026

NCT05842057[a]	Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER)	240	Aug 2028
NCT06150209[a]	A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients	100	Jun 2025
NCT05796765[a]	A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee	43 (terminated)	Dec 2023
Unpublished			
NCT03855514[a]	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield®‡ and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers	200	Dec 2021
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN®‡ Injection in Patients With Rotator Cuff Tear	100	Sep 2022

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

References

1. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine?. Regen Med. Mar 2009; 4(2): 275-91. PMID 19317646
2. Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. Oct 2013; 10(5): 493-500. PMID 23902526
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(I):167-177.

4. U.S. Food and Drug Administration. Public Safety Notification on Amniotic Fluid Eyedrops. October 17, 2024. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-amniotic-fluid-eyedrops.
5. U.S. Food and Drug Administration. Warning Letters. 2025. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters.
6. U.S. Food and Drug Administration. Warning Letter: Integra LifeSciences Corporation. December 19, 2024. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/integra-lifesciences-corporation-698850-12192024.
7. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. 2017 https://www.regulations.gov/document?D=FDA-2017-D-6146-0003
8. Food and Drug Administration. 510(k) Summary: ProKeraTM Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf.
9. Cazzell SM, Caporusso J, Vayser D, et al. Dehydrated Amnion Chorion Membrane versus standard of care for diabetic foot ulcers: a randomised controlled trial. J Wound Care. Jul 01 2024; 33(Sup7): S4-S14. PMID 38973638
10. Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. J Comp Eff Res. Jan 2020; 9(1): 23-34. PMID 31691579
11. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. Wound Repair Regen. May 2018; 26(3): 274-283. PMID 30098272
12. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. Feb 2019; 16(1): 122-130. PMID 30246926
13. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. Dec 2018; 15(6): 950-957. PMID 30019528
14. Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds. Mar 2016; 28(3): 70-7. PMID 26978860
15. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. Dec 2015; 12(6): 724-32. PMID 25424146
16. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. Apr 2016; 13(2): 272-82. PMID 26695998

17. Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. Feb 2019; 16(1): 19-29. PMID 30136445
18. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix(®) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. Oct 2014; 11(5): 554-60. PMID 25048468
19. Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. Jun 2015; 27(6): 158-69. PMID 26061491
20. Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. Int Wound J. Jun 2017; 14(3): 569-577. PMID 27489115
21. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014; 22(6): 688-93. PMID 25224019
22. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix ®) allograft for the treatment of venous leg ulcers. Int Wound J. Feb 2018; 15(1): 114-122. PMID 29024419
23. Bianchi C, Tettelbach W, Istwan N, et al. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. Jun 2019; 16(3): 761-767. PMID 30864259
24. Serena TE, Orgill DP, Armstrong DG, et al. A Multicenter, Randomized, Controlled, Clinical Trial Evaluating Dehydrated Human Amniotic Membrane in the Treatment of Venous Leg Ulcers. Plast Reconstr Surg. Nov 01 2022; 150(5): 1128-1136. PMID 36067479
25. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. Aug 2016; 29(6): 443-50. PMID 26683979
26. Pill SG, Ahearn B, Tokish JM, et al. Amniotic Tissue Injections Are an Effective Alternative to Corticosteroid Injections for Pain Relief and Function in Patients With Severe Knee Osteoarthritis: A Double-Blind, Randomized, Prospective Study. J Am Acad Orthop Surg Glob Res Rev. Jan 01 2025; 9(1). PMID 39813395
27. Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. Br J Sports Med. Nov 2016; 50(22): 1367-1375. PMID 27143138
28. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. Oct 2013; 34(10): 1332-9. PMID 23945520
29. Cazzell S, Stewart J, Agnew PS, et al. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. Foot Ankle Int. Oct 2018; 39(10): 1151-1161. PMID 30058377

30. Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. Eye Contact Lens. Sep 2013; 39(5): 341-7. PMID 23945524
31. Liu J, Li L, Li X. Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis. Cornea. Apr 2019; 38(4): 454-462. PMID 30702468
32. Yin HY, Cheng AMS, Tighe S, et al. Self-retained cryopreserved amniotic membrane for treating severe corneal ulcers: a comparative, retrospective control study. Sci Rep. Oct 12 2020; 10(1): 17008. PMID 33046729
33. Paris Fdos S, Gonçalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. Aug 2013; 97(8): 980-4. PMID 23723410
34. Kheirkhah A, Casas V, Raju VK, et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am J Ophthalmol. May 2008; 145(5): 787-94. PMID 18329626
35. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. Eye Contact Lens. Jul 2009; 35(4): 172-5. PMID 19474753
36. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens-Johnson Syndrome: A Randomized Control Trial. Ophthalmology. Mar 2016; 123(3): 484-91. PMID 26686968
37. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. Ocul Surf. Jul 2004; 2(3): 201-11. PMID 17216092
38. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 2017: 6404918. PMID 28894606
39. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328
40. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. Feb 2011; 95(2): 199-204. PMID 20675729
41. Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial. Am J Ophthalmol. Mar 2019; 199: 209-215. PMID 30419194
42. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. Nov 2005; 112(11): 1963-9. PMID 16198422
43. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. Ophthalmology. Jan 2013; 120(1): 201-8. PMID 23062647
44. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. Feb 11 2016; 2(2): CD011349. PMID 26867004
45. Toman J, Michael GM, Wisco OJ, et al. Mohs Defect Repair with Dehydrated Human Amnion/Chorion Membrane. Facial Plast Surg Aesthet Med. 2022; 24(1): 48-53. PMID 34714143

46. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. Feb 2016; 63(2 Suppl): 3S-21S. PMID 26804367
47. Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2016; 24(1): 112-26. PMID 26663430

Policy History

Original Effective Date: 08/19/2015
Current Effective Date: 07/01/2025

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

	Added the requirement that "patient agrees to comply with adequate mechanical offloading" for initial placement and similarly for continued treatment eligible for coverage criteria for additional applications, adding that "patient remains compliant with adequate mechanical offloading". Revised the Policy Guidelines definition of non-healing diabetic wounds was revised to "an ulcer that fails to demonstrate > 50% wound area reduction after a minimum of 4 weeks of standard wound therapy." It replaces the previous definition that was worded as "fails to demonstrate 20% decrease in wound area with standard wound care for at least 2 weeks."
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Brought back for clarification.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. AmnioGraft, Vendaje Optic and Artacent Ocular was added as eligible for coverage for HAM grafts with or without suture or glue. Added new investigational statement for repair following Mohs micrographic surgery.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2023	Coding update
09/20/2023	Coding update
09/27/2023	Added NuDYN®‡ DL MESH and NuDYN®‡ SLW to the PG2 table listing investigational amniotic products that have an HCPCS code
01/01/2024	Table PG 2 updated due to new codes. Coding update: Add new HCPCS codes.
03/27/2024	Coding update
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. AmnioExcel added to the list of eligible for coverage products for the treatment of nonhealing diabetic lower-extremity ulcers. Products in table PG 1 revised.
06/14/2024	Coding update, PG1 and PG2 content and format revised.
10/01/2024	Coding update. PG 2 content updated.
01/01/2025	Coding update. PG 2 content updated.
04/01/2025	Coding update. PG 2 content updated.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. NuShield added to existing medically necessary policy statement for the treatment of nonhealing diabetic lower-extremity ulcers based on randomized controlled trials evidence. Removed NuShield and HCPCS Code Q4160 from PG 2 Table and moved it to PG 1 Table. Removed Derm-Maxx and HCPCS Code Q4238 from the PG 2 Table.
07/01/2025	Coding update. PG 2 content updated.

Next Scheduled Review Date: 06/2026

Policy # 00458
Original Effective Date: 08/18/2015
Current Effective Date: 07/01/2025

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 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.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	15271, 15275, 17999, 65778, 65779, 65780, 66999
HCPCS	A2001, A2035, A4100, Q4100, Q4126, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4176, Q4177, Q4178, Q4179, Q4180, Q4181, Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4199, Q4201, Q4204, Q4205, Q4206, Q4208, Q4209, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221, Q4224, Q4225, Q4227, Q4229, Q4230, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4239, Q4240, Q4241, Q4242, Q4245, Q4246, Q4247, Q4248, Q4249, Q4250, Q4251, Q4252, Q4253, Q4254, Q4255, Q4256, Q4257, Q4258, Q4259, Q4260, Q4261, Q4262, Q4263, Q4264, Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271, Q4272, Q4273, Q4274, Q4275, Q4276, Q4278, Q4279, Q4280, Q4281, Q4282, Q4283, Q4284, Q4285, Q4286, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, Q4304, Q4305, Q4306, Q4307, Q4308, Q4309, Q4310, Q4311, Q4312, Q4313, Q4314, Q4315, Q4316, Q4317, Q4318,

	Q4319, Q4320, Q4321, Q4322, Q4323, Q4324, Q4325, Q4326, Q4327, Q4328, Q4329, Q4330, Q4331, Q4332, Q4333, Q4334, Q4335, Q4336, Q4337, Q4338, Q4339, Q4340, Q4341, Q4342, Q4343, Q4345, Q4346, Q4347, Q4348, Q4349, Q4350, Q4551, Q4352, Q4553, Q4354, Q4355, Q4356, Q4357, Q4358, Q4359, Q4360, Q4361, Q4362, Q4363, Q4364, Q4365, Q4366, Q4367, V2790 Delete codes effective 07/01/2024: Q4210, Q4277 Delete codes effective 04/01/2025: Q4231 Add codes effective 07/01/2025: Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4378, Q4379, Q4380, Q4382
ICD-10 Diagnosis	All related diagnoses

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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

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

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

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

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

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

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.