Skin and Tissue Substitutes

MEDICAL POLICY NUMBER: 16

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Notice to Medicaid Policy Readers: For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's prioritized list for the following coverage guidelines:

Skin and Tissue Substitutes: Guideline Note 163

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Medically Necessary Skin and Tissue Substitutes by Indication

Note: This policy does not apply to the following products for vocal cord paralysis treatment, which may be considered medically necessary: Cymetra; Integra™ Flowable Wound Matrix.

I. FDA approved allogenic Acellular Dermal Matrix (ADM) products may be considered **medically necessary** when used for a medically necessary breast reconstruction surgery.
   A. This includes but is not limited to the following products: AlloDerm®; Dermacell™; FlexHD® Accellular Hydrated Dermis.

II. FDA approved biosynthetic dressing products may be considered **medically necessary** as a treatment of burn wounds when **both** of the following (A.-B.) criteria are met. This includes, but is not limited to Biobrane/Biobrane-L.
   A. The skin substitute is used as a temporary covering of a partial-thickness burn (See description section for definition); **and**

B. Applied to freshly debrided or excised wounds, or meshed autografts containing less than 105 bacteria/g tissue

III. FDA approved cultured epidermal autograft products may be considered **medically necessary** when used in accordance with the U.S. Food and Drug Administration Humanitarian Device Exemption for adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area greater than or equal to 30%. This includes but is not limited to Epicel.

IV. FDA approved dermal regeneration and bilayer products may be considered **medically necessary** as a treatment of burn wounds when **both** of the following (A.-B.) criteria are met. This includes but is not limited to the following products: Integra® Dermal Regeneration; Integra® Omnigraft Dermal Regeneration Matrix; Integra® Bilayer Matrix Wound Dressing; Integra® Meshed Bilayer Wound Matrix.

A. To be used for the post-excisional treatment of life-threatening full thickness or deep partial-thickness thermal injuries (See description section for definition); **and**
B. Sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.

V. FDA approved human fibroblast-derived temporary skin substitute may be considered **medically necessary** when used as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement. This includes but is not limited to TransCyte®.

Diabetic Foot Ulcers

Products	Medical Necessity Criteria

• Apligraf® • Allopatch • AmnioBand Membrane • Dermagraft® • EpiFix® Amniotic Membrane • Grafix® Core/Grafix® Prime/ Grafix® PL Prime/ Grafix® Plus • GraftJacket® Regenerative Tissue Matrix • Integra® Dermal Regeneration Template • Integra™ Omnigraft Dermal Regeneration Matrix • Oasis® Wound Matrix/Oasis® Ultra Tri-Layer Matrix • TheraSkin®	VI. The products listed in the left column may be considered **medically necessary** for the treatment of diabetic foot ulcers when **all** of the following (A.-H.) criteria are met: A. The skin substitute is used in conjunction with standard diabetic ulcer care; **and** B. The ulcer extends through the dermis <u>but without</u> tendon, muscle, joint, or bone exposure; **and** C. The ulcer is at least $1cm^2$ but no more than $25cm^2$; **and** D. The ulcer is free of infection; **and** E. The patients A1c (HbA1C) level is less than 12%; **and** F. Failure of at least 4 weeks of standard diabetic foot ulcer therapy (e.g., surgical debridement, dressing changes); **and** G. The foot to be treated has adequate blood supply as defined by **at least one** of the following (1.-2.) criteria: 1. Ankle-brachial index (ABI) of ≥ 0.70; **and/or** 2. The presence of a palpable pedal pulse; **and** H. The skin substitute is limited to no more than 5 applications, at a minimum of 1 week between applications, over the course of 12 weeks. (Except GraftJacket® Regenerative Tissue Matrix [Q4107] which is limited to only 1 initial application.)

Venous Status Ulcers

Products	Medical Necessity Criteria

• Apligraf® • EpiFix® Amniotic Membrane • Oasis® Wound Matrix • TheraSkin®	VII. The products listed in the left column may be considered **medically necessary** for the treatment of venous stasis ulcers when **all** of the following (A.-G.) criteria are met: A. The skin substitute is used in conjunction with standard venous stasis ulcer care; **and** B. The ulcer extends through the dermis but without tendon, muscle, joint, or bone exposure; **and** C. The ulcer is at least 2cm^2 but no more than 20cm^2; **and** D. The ulcer is free of infection; **and** E. Failure of at least 4 weeks of standard venous stasis ulcer therapy (e.g., compression therapy); **and** F. The leg to be treated has adequate blood supply as defined by **at least one** of the following (1.-2.) criteria: G. Ankle-brachial index (ABI) of ≥ 0.70; **and/or** H. The presence of a palpable pedal pulse; **and** I. The skin substitute is limited to no more than 5 applications, at a minimum of 1 week between applications, over the course of 12 weeks.

Traumatic Wounds

VIII. The use of the following FDA approved skin and tissue substitute products may be considered **medically necessary** for the treatment of traumatic wounds when autografting is not possible:

- A. Biosyntehetic dressing products (including Biobrane®/Biobrane®-L)
- B. Cultured epidermal autograft products (including Epicel)
- C. Integra dermal regeneration and bilayer products:
  1. Integra® Dermal Regeneration Template
  2. Integra® Omnigraft Dermal Regeneration Matrix
  3. Integra® Bilayer Matrix Wound Dressing
  4. Integra® Meshed Bilayer Wound Matrix
- D. Human fibroblast derived temporary skin substitute (including TransCyte®)

Skin and Tissue Substitutes as a Component of Genital Surgery

IX. The use of a skin substitute as a component of a genital surgery may be **medically necessary** for surgical wound coverage prior to skin grafting. Member must meet medical necessity criteria for gender affirming surgery.

Skin Substitutes for prevention of Frey's Syndrome after Parotidectomy

X. The use of a skin substitute may be **medically necessary** to prevent Frey's Syndrome after parotidectomy.

Repeat Treatment

XI. Repeat treatment (i.e. any additional applications after the initial 12-week treatment period outlined in criteria VI. And VII. above) of diabetic foot ulcers or venous stasis ulcers using skin and tissue substitutes may be considered **medically necessary** when the ulcer continues to improve on the basis of wound documentation. Wound documentation must include **all** of the following (A.-C.):

A. The number and position of ulcers; **and**
B. Wound measurements for each ulcer, including all of the following (1.-3.):
   1. Length; **and**
   2. Width; **and**
   3. Depth; **and**
C. Descriptions of wound edge parameters, wound base quality, drainage, and infection.

Non-Covered Indications

XII. The use of skin and tissue substitutes is considered **not medically necessary** when the medically necessary indication and/or product and/or criteria above are not met, including, but not limited to:

A. Complex nasal reconstruction
B. Tympanic membrane perforation
C. Hernia repair
D. Rotator cuff tear repair
E. Repair of non-traumatic surgical excision of skin/soft tissue mass/lesion (e.g., Mohs surgery for squamous or basal cell carcinomas)

Not Medically Necessary Skin Substitutes

XIII. Skin and tissue substitute products not listed in the tables above are considered **not medically necessary**, including, but not limited to, the following:

Products		
AC5® Topical Gel	Cryo-cord	Novafix
Affinity	Cygnus™	NovoSorb
Allogen	Cymetra *Note: May be medically necessary for the treatment of vocal cord paralysis.*	NuCel™
Alloskin™ AC	Cytal®	NuDYN® NuDYN® DL NuDYN® DL MESH NuDYN® SL NuDYN® SLW
Alloskin™ RT	Dermacell™	NuShield™
Allowrap™	Dermacyte Amniotic Membrane	Oasis® Burn Matrix

Altiply	Dermabind	Omeza collagen matrix
AmnioAMP-MP	Derma-gide	Orion
AmnioArmorAmnioAMP-MP	DermaMatrix Acellular Dermis	PalinGen®/Promatrx®
AmnioBand® ParticulateAmnioArmor	Derm-maxx	PalinGen® Xplus
AmniobindAmnioBand® Particulate	DermaPure™	Permacol™
Amnion Bio/AxobiomembraneAmniobind	DermaSpan™	Permeaderm
AmniocoreAmnion Bio/Axobiomembrane	Dermavest	Phoenix wound matrix
Amniocyte PlusAmniocore	Durepair Regeneration Matrix®	PriMatrix™
AmnioEXCEL™/BiodExcel™Amniocyte Plus	Endoform Dermal Template™	Procenta
AmnioFix®AmnioEXCEL™/BiodExcel™	ENDURAGen	Progenamatrix
AmnioMatrix®/BioMatrix®AmnioFix®	Enverse	Protext
Amnio-maxx/Amnio-maxx LiteAmnioMatrix®/BioMatrix®	Epifix® Injectable	PuraPly™/PuraPly™ AM
AmnioPro-AAmnio-maxx/Amnio-maxx Lite	EpiCord™	ReCell
Amniorepair	Epieffect	Reguard
AmniotextAmnioPro-A	Esano	Release
Amniotext PatchAmniorepairAmnioPro-A	Excellagen®	Repriza®Reguard
Amnio WoundAmniotextAmniorepair	E-Z Derm™	Restorigin™ MembraneRelease
		Resolve Matrix™
Amniowrap2Amniotext PatchAmniotext	FloGraft™	Restorigin™ FluidRepriza®
AmniplyAmnio WoundAmniotext Patch	Floweramnio™ Flo	RestrataRestorigin™ Membrane
ApisAmniowrap2Amnio Wound	Floweramnio™ Patch	Revita®Restorigin™ Fluid
Architect™/Architect™ PX/Architect™ FX/Architect™ Extracellular MatrixAmniplyAmniowrap2	Flowerderm™	Revitalon™Restrata
Artacent™ AC PowderApisAmniply	Fluid Flow™	Signature APatchRevita®
Artacent™ AC GraftArchitect™/Architect™	GalaFLEX, Galaflex Mesh, Galaflex Scaffold	SkinTE™Revitalon™

PX/Architect™ FX/Architect™ Extracellular MatrixApis		
Artracent™ CordArtacent™ AC PowderArchitect™/Architect™ PX/Architect™ FX/Architect™ Extracellular Matrix	GammaGraft	Strattice™Signature APatch
ArthroFlex™Artacent™ AC GraftArtacent™ AC Powder	Genesis Amniotic Membrane	StravixSkinTE™
AscentArtracent™ CordArtacent™ AC Graft	Graftjacket® Xpress	SuredermStrattice™
Axolotl Graft/Axolotl DualgraftArthroFlex™Artracent™ Cord	Helicoll™	SurgicordStravix
Axolotl Ambient/Axolotl CryoAscentArthroFlex™	hMatrix®	SURGIgraft™Surederm
Barrera	Human Health Factor 10 Patch	SURGIgraft™ DualSurgicord
BellaCell HDAxolotl Graft/Axolotl DualgraftAscent	Hyalomatrix®Human Health Factor 10 Patch	SurgraftSURGIgraft™Surgicord
Bio-conneKt™ Wound MatrixAxolotl Ambient/Axolotl CryoAxolotl Graft/Axolotl Dualgraft	InnovamatrixHyalomatrix®	Supra SDRMSURGIgraft™ DualSURGIgraft™
BioDesign® Otologic Repair GraftBellaCell HDAxolotl Ambient/Axolotl Cryo	Integra™ MatrixInnovamatrix	SuprathelSurgraftSURGIgraft™ Dual
BioDfactor™Bio-conneKt™ Wound MatrixBellaCell HD	Integra™ Flowable Wound Matrix *<u>Note</u>: May be medically necessary for the treatment of vocal cord paralysis.*Integra™ Matrix	SurfactorSupra SDRMSurgraft
BioDfence™BioDesign® Otologic Repair GraftBio-conneKt™ Wound Matrix	Interfyl™Wound careIntegra™ Flowable Wound Matrix *<u>Note</u>: May be medically necessary for the treatment of vocal cord paralysis.* InnovaBurn® InnovaMatrix® XL InnovaMatrix® PD	SymphonySuprathelSupra SDRM
BioDfence™ DryflexBioDfactor™BioDesign® Otologic Repair Graft	Keramatrix®Wound careInterfyl™Wound care	TAGSurfactorSuprathel
Bionext PatchBioDfence™BioDfactor™	Kerecis Omega3Soft tissue repairKeramatrix®Wound care	Talymed™SymphonySurfactor

BioVance®BioDfence™ DryflexBioDfence™	Kerecis Omega3 WoundKerecis Omega3Soft tissue repair	TenoGlide®TAGSymphony
BioWound/Bio Wound Plus/BioWound XplusBionext PatchBioDfence™ Dryflex	KeroxxWound care Soft tissue repairKerecis Omega3 Wound	TenSIX™Talymed™TAG
CarepatchBioVance®Bionext Patch	MariStem® MicromatrixSurgical barrier Tendon repairKeroxxWound care Soft tissue repair	TheragenesisTenoGlide®Talymed™
CeleraBioWound/Bio Wound Plus/BioWound XplusBioVance®	Matrion™ Surgical barrier Tendon repairMariStem® MicromatrixSurgical barrier Tendon repair	TruSkin™TenSIX™TenoGlide®
Cellesta™ Amniotic MembraneCarepatchBioWound/Bio Wound Plus/BioWound Xplus	Matrix HD™Wound careMatrion™ Surgical barrier Tendon repair	VendajeTheragenesisTenSIX™
Cellesta™ CordCeleraCarepatch	Mediskin™Wound careMatrix HD™Wound care	Veritas Collagen MatrixTruSkin™Theragenesis
Cellesta™ Flowable AmnionCellesta™ Amniotic MembraneCelera	MemoDerm™Wound careMediskin™Wound care	VIMVendajeTruSkin™
Clarix® FloCellesta™ CordCellesta™ Amniotic Membrane	Microlyte MatrixWound careMemoDerm™Wound care	WoundEx/BioskinVeritas Collagen MatrixVendaje
Cogenex Amniotic MembraneCellesta™ Flowable AmnionCellesta™ Cord	MirragenWound careMicrolyte MatrixWound care	WoundEx Flow/Bioskin FlowVIMVeritas Collagen Matrix
	Miro3D Wound Matrix	
Cogenex Flowable AmnionClarix® FloCellesta™ Flowable Amnion	Miroderm™Surgical barrier Wound careMirragenWound care	Woundfix/Woundfix Plus/Woundfix XplusWoundEx/BioskinVIM
Coll-e-DermCogenex Amniotic MembraneClarix® Flo	MLG-CompleteWound careMiroderm™Surgical barrier Wound care	XcellerateWoundEx Flow/Bioskin FlowWoundEx/Bioskin
Complete™Cogenex Flowable AmnionCogenex Amniotic Membrane	MyOwn SkinWound careMLG-CompleteWound care	XcellistemWoundfix/Woundfix Plus/Woundfix XplusWoundEx Flow/Bioskin Flow
Conexa™Coll-e-DermCogenex Flowable Amnion	Neopatch™Integumental tissue repairMyOwn SkinWound care	XCM Biologic Tissue MatrixXcellerateWoundfix/Woundfix Plus/Woundfix Xplus
CorecyteComplete™Coll-e-Derm	NeoStimNeopatch™Integumental tissue repair	XWRAP®XcellistemXcellerate

CoretextConexa™Complete™	NEOX® 100 Quick-Peel Wound MatrixWound careNeoStim	Zenith Amniotic MembraneXCM Biologic Tissue MatrixXcellistem
CorMatrixCorecyteConexa™	NEOX® 1k Wound MatrixTissue repairNEOX® 100 Quick-Peel Wound MatrixWound care	XWRAP®XCM Biologic Tissue Matrix
CorplexCoretextCorecyte	NEOX® FLOTissue repairNEOX® 1k Wound MatrixTissue repair	Zenith Amniotic MembraneXWRAP®
CorMatrixCoretext	NeoMatriX® Wound MatrixNEOX® FLOTissue repair	Zenith Amniotic Membrane
CorplexCorMatrix	NovachorTendon repairNeoMatriX® Wound Matrix	
Corplex	NovachorTendon repair	

Link to Evidence Summary

POLICY CROSS REFERENCES

- Cosmetic and Reconstructive Surgery, MP98
- Breast Surgery: Reduction Mammoplasty, Reconstructive Surgery, and Implant Management, MP58
- Gender Affirming Surgical Interventions, MP32

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

Medical records documentation must clearly support the medical necessity of bioengineered skin and tissue substitutes. This would include the following:

- Characteristics of the wound/ulcer
- Wound/ulcer measurement
- Evidence of prior ineffective standard care, including the duration of this treatment
- The presence of qualifying or disqualifying conditions (i.e., HbA1C levels, ankle-brachial index [ABI])

BACKGROUND

Burn Wounds

Burn injuries are classified by the depth of the wound.[1]

- First-degree burns involve only the epidermal layer (the outermost layer of skin). These burns heal completely within several days.
- Second-degree (partial-thickness) burns involve the epidermis and only part of the dermis (the thick layer of living tissue below the epidermis that forms the true skin, containing blood capillaries, nerve endings, sweat glands, hair follicles, and other structures). These burns may heal spontaneously, although healing usually requires reepithelialization from adjacent unburned skin or skin substitutes.
- Third-degree (full-thickness) burns involve all of the epidermal and dermal layers, with varying amounts of the sub-cutaneous layer. These burns cannot heal spontaneously and thus require excision and grafting.
- Fourth-degree burns involve deep structures such as tendon, muscle, and bone.

The successful treatment of burn wounds requires timely restoration of the skins protective function. "Conventionally, autologous split or full-thickness skin grafts have been recognized as the best definitive burn wound coverage, but it is constrained by the limited available sources, especially in major burns. Donor site morbidities in term of additional wounds and scarring are also of concern of the autograft application."[2] Skin substitutes are necessary for both acute burn wounds and in patients requiring extensive reconstruction post-burn.

Diabetic Foot Ulcer

Chronic foot ulcers are common in hyperglycemia or undiagnosed poorly controlled diabetes due to damage of nerves (neuropathy), blood vessels (poor blood flow), and other body systems. "Approximately 85% of lower limb amputations among people with diabetes are preceded by a foot ulcer."[3] Diabetes-related foot ulcers are diagnosed by clinical evaluation and are classified based on the ulcer size, depth, and presence of an infection. The Wagner Ulcer Classification System is the most commonly used:

- Grade 0: No open lesions; may have deformity of cellulitis
- Grade 1: Superficial diabetic ulcer (partial- or full-thickness)
- Grade 2: Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
- Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis
- Grade 4: Gangrene localized to portion of forefoot or heel
- Grade 5: Extensive gangrenous involvement of the entire foot[3]

Treatment includes vascular and wound assessment, infection control, debridement, dressing changes, and offloading. "Offloading is the use of devices to reduce pressure on the wound, such as casts, removable cast walkers, and special shoes."[3] Amputation is required when diabetic foot ulcers do not respond to treatment or become infected.

Venous Stasis Ulcer

Venous stasis ulcers, also known as venous leg ulcers or varicose ulcers, "are partial or full-thickness defects of an area of the skin in the lower leg, usually between the knee and the ankle, due to valvular incompetence and venous reflux causing venous hypertension."[4] These ulcers are common in older patients, women, and patients with conditions causing chronic venous insufficiency (e.g., congestive heart failure) and/or venous damage (e.g., injection drug use). Longer wound duration and larger wound

surface area are associated with poor ulcer healing. "Standard care for venous leg ulcers typically includes wound care and compression therapy. Wound care may include cleansing, debridement, infection control, dressing, and bandaging."[4] In patients whose venous stasis ulcers do not heal despite standard care, venous surgery to correct underlying venous pressure may be required.

Skin Substitutes

Skin substitutes, also known as bioengineered, tissue-engineered, or artificial skin, are intended to protect wounds and reconstruct defective, ulcerated tissue.[4] They function by physically covering wounds and providing structure to induce tissue regeneration and subsequent wound healing. They are generally classified into three main types:

1. Cellular—composed of living cells; or
2. Acellular—composed of synthetic materials or tissue from which living cells have been removed; or
3. A combination of cellular and acellular components.

Cellular skin substitutes are further categorized as follows:

- Autograft: A sample of the patient's own healthy skin is harvested and placed in the ulcer
- Allografts: Skin or tissue harvested from another human (e.g., cadaver)
- Xenograft: Skin or tissue is harvested from an animal with similar skin structure (e.g., pigs).

Although there are many different types of skin substitutes, they are all similarly used as an adjunct to standard wound care. Application of a skin substitute requires that no infection be present, the wound bed is properly prepared, and the wound has achieved hemostasis.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

Depending on the purpose or function of the skin substitute, FDA regulation is through the premarket approval (PMA) process or 510(k) premarket notification process. Products derived from donated human tissue are overseen by the FDA regulations for banked human tissue and the American Association of Tissue Banks (AATB) guidelines.

PMA Process

Skin substitutes that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA process as a class III, high-risk device. These are considered interactive because they actively promote healing by interacting directly or indirectly with body tissues.

510(k) Premarket Notification Process

Skin substitutes approved under the 510(k) premarket notification processes are typically those whose primary purpose is to protect the wound and provide a foundation for proper healing. These skin substitutes may or may not interact with body tissues.

FDA Regulations for Tissue and Tissue Products

Donated skin or tissue "intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P."[5] The Center for Biologics Evaluation and Research (CBER) regulates HCT/Ps under 21 CFR Parts 1270 and 1271.

The following products are addressed in the policy criteria above as medically necessary for breast reconstruction, burn wounds, diabetic foot ulcers, or venous stasis ulcers.

Products	Indications for Use
AlloDerm®[6]	AlloDerm is to be used for repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument.
Apligraf®[7]	• Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. • Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule, or bone exposure.
Biobrane®/Biobrane®-L[8,9]	• Temporary wound dressing for coverage of superficial burns, donor sites and meshed autographs. • Application should be to freshly debrided or excised wounds, or meshed autografts containing less than 105 bacteria/g tissue. • The debridement or excision must be done thoroughly to remove all coagulum or eschar. BIOBRANE/BIOBRANE-L will not adhere to dead tissue and any remaining necrotic tissue may cause infection. • Establish hemostatis prior to application of BIOBRANE/BIOBRANE-L. • Apply fabric (dull) side down, wrinkle-free against the wound surface with slight tension. • If less secondary adherence is desired (e.g. deeper donor sites or meshed autografts), BIOBRANE-L is recommended.

	• Under slight tension immobilize BIOBRANE/BIOBRALE-L using staples, tape, sutures, or skin closure strips and wrap area with dry gauze dressing or other stenting device to hold the dressing firmly in contact with the wound surface for 24 to 36 hours.
Dermacell™[10]	Intended for use as bio-implant during breast reconstruction surgery or during the treatment of chronic wounds.
Dermagraft®[11]	Dermagraft is indicated for use in the treatment of full-thickness diabetic foot ulcers greater than six weeks duration, which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure. Dermagraft should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot.
Epicel[12]	Epicel is indicated for use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.
EpiFix® Amniotic Membrane[13]	EpiFix is an amnion/chorion membrane allograft for acute and chronic wound care.
FlexHD® Acellular Hydrated Dermis[14]	FlexHD is used for the replacement of damaged or inadequate integumental tissue or for the repair, reinforcement, or supplemental support of soft tissue defects.
Grafix®[15]	Grafix is a cryopreserved placental membrane comprised of an extracellular matrix (ECM) rich in collagen, growth factors, fibroblasts, mesenchymal stem cells (MSCs), and epithelial cells native to the tissue. Designed for application directly to acute and chronic wounds with a flexible, conforming cover that adheres to complex anatomies.
GraftJacket™ Regenerative Tissue Matrix[16]	The GRAFTJACKET™ Matrix is used to provide supplemental support, protection, and reinforcement of tendon and ligamentous tissue; to be used as a periosteal patch or covering; or for protection and support of bone and tendons in foot & ankle and hand surgery.
Integra® Dermal Regeneration Template/Omnigraft® Dermal Regeneration Matrix [17]	The original PMA (P900033), Integra Dermal Regeneration Template (Integra Template) was approved for post-excisional treatment of life-threatening full thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient. Another indication was added (supplement S042) for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. Integra Template is also marketed as Integra Omnigraft Dermal Regeneration Matrix (Omnigraft), specifically for the indication

	in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
− Integra® Bilayer Matrix Wound Dressing[18] − Integra® Meshed Bilayer Wound Matrix[19]	The Integra Bilayer Matrix Wound Dressing and the Integra Meshed Bilayer Wound Matrix Dressing are substantially equivalent to the Integra Dermal Regeneration Template. These products are indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.
Oasis® Wound Matrix[20]	The OASIS® Wound Matrix device's intended use is for the management of wounds including: • partial and full-thickness wounds, • pressure ulcers, • venous ulcers, • diabetic uicers, • chronic vascular ulcers, • tunneled/undermined wounds, • surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), • trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), • draining wounds.
TheraSkin®[21]	TheraSkin is a biologically active, cryopreserved real human skin allograft, composed of living cells, fibroblasts and keratinocytes, and a fully developed extra cellular matrix (ECM) in its epidermis and dermis layers. TheraSkin can be used on chronic wounds with exposed muscle, bone, tendon and joint capsule including, but not limited to, DFUs, VLUs, Arterial ulcers, dehisced surgical wounds, pressure sores and wounds that might otherwise require an autograft.
TransCyte®[22]	Indicated for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement; and for the treatment of mid-dermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting.

Humanitarian Device Exemption (HDE)[23,24]

HDE is a special FDA approval that allows a device to be marketed on a limited basis provided that:

1. The device is used to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year
2. The device would not be available to a person with such a disease or condition unless the exemption is granted
3. No comparable device is available to treat or diagnose the disease or condition; and
4. The device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment

HDE applications are not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. The labeling must also indicate that the effectiveness of the device for the specific indication has not been demonstrated.

Humanitarian use devices may only be used in facilities that have obtained an institutional review board (IRB) approval to oversee the usage of the device in the facility, and after an IRB has approved the use of the device to treat or diagnose the specific rare disease. The HDE holder (defined as the person who or entity that obtains the approval of an HDE from FDA) is responsible for ensuring that a device approved under an HDE is administered only in facilities having an IRB constituted and acting in accordance with the FDA's regulation governing IRBs (21 CFR Part 56), including continuing review of use of the device.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of skin substitutes for breast reconstruction, burn wounds, diabetic foot ulcers, or venous stasis ulcers. Below is a summary of the available evidence identified through December 2023.

Systematic Reviews

- In 2020, and reviewed in 2023, Hayes conducted a comparative effectiveness review to evaluate cellular skin substitutes for chronic foot ulcers in adults with diabetes mellitus.[3] The evidence review identified 11 randomized controlled trials (RCT) and 2 observational retrospective database studies as eligible for inclusion. Sample sizes ranged from 23 to 180 participants in the RCTs, while the 2 observational studies assessed data from 20,482 and 13,193 patients. Outcome measures included incidence of complete ulcer closure, time to complete ulcer closure, incidence of amputation, and quality of life (QOL). Studies compared cellular skin substitutes to standard wound therapy, other cellular skin substitutes, acellular substitutes, and standard wound therapy plus acellular skin substitutes.

  Four studies reported on incidence of amputation. Two RCTs compared incidence of amputation posttreatment with 1 of 2 cellular substitutes, Hyalograft/Laserskin or Grafix, with standard wound care, and found no difference in incidence, with extremely low incidences in all groups. One retrospective study found Apligraf to significantly reduce the need for amputation compared to

standard wound care (11.8% versus 16.3%, respectively). The other retrospective study compared 2 cellular skin substitutes and 2 acellular skin substitutes, and found differences in amputation incidence among the 4 treatments, ranging from 7% to 10.1%, but no pairwise analysis was performed.

Eleven studies reported on the incidence of complete ulcer healing. In the 6 studies comparing cellular skin substitutes to standard wound care alone, incidence of complete healing ranged from 24% to 89% in the cellular substitutes group and 21% to 69% in standard care group. Five of the 6 studies reported a statistically greater incidence of complete ulcer healing in the cellular group, while one study found no difference. In 3 studies comparing different cellular skin substitutes, 1 RCT found a significantly higher incidence of complete healing the Apligraf group compared to TheraSkin. Another trial found early benefit of TheraSkin versus Dermagraft, but the significant difference diminished at follow up. The third study found no difference in healing between Grafix and Dermagraft. Four studies compare complete ulcer healing between cellular and acellular skin substitutes. One RCT found no significant difference between Dermagraft and MatriStem (acellular). Another RCT found healing rates were higher in the Epifix (acellular) group compared to Apligraf. A third RCT found higher rates in the Amnioband group (acellular) compared with Apligraf group. The fourth study, a retrospective analysis, found higher healing rates with 2 acellular substitutes (MatriStem and Oasis) compared to Apligaf and Dermagraft.

Strengths of these studies included the randomized controlled design, large sample sizes, masked outcome assessors, and using computer programs to assess wound size and/or closure. Limitations are present in the short follow-up duration of some studies and inadequate number of patients to attain adequate power. Ultimately, Hayes concluded the following rating:

- C—"For use of cellular skin substitutes as an adjunct to standard wound care (SWC) to treat chronic, uninfected diabetes-associated foot ulcers (DFUs) that have not healed with SWC alone in adults with well-controlled blood glucose and adequate blood flow to the extremities"[3]

- In 2020 (and reviewed in 2023) Hayes conducted a comparative effectiveness review of acellular skin substitutes for chronic foot ulcers in adults with diabetes mellitus.[25] The report included 13 RCTs and one observational retrospective study in their review. Hayes deemed 5 RCTS to be good quality, 5 of fair quality, and 3 of poor quality.

  Similar to the report on cellular substitutes, no significant differences in incidence of amputation were found comparing acellular skin substitutes and standard wound care, based on one RCT. Eleven studies compared incidence of complete ulcer healing after acellular skin substitutes versus standard wound care, with 10 finding acellular substitutes to have higher incidence (14.3% to 97% in acellular groups versus 0% to 91% in standard care groups) and one study that did not analyze results. In 4 studies that compared healing rates between acellular and cellular skin substitutes, one RCT found no difference (MatriStem [acellular] v Dermagraft), while two other RCTs and one retrospective study found acellular to have higher rates of complete healing. EpiFix (acellular) had significantly higher healing rates compared to Apligraf (cellular), Amnioband (acellular) had significantly higher rates compared to Apligraf, and MatriStem and Oasis acellular skin substitutes performed better than Apligraf and Dermagraft cellular substitutes.

The overall quality of evidence among the studies was low to very low, due to limitations an individual studies, including follow up time, sample sizes, and risks of bias due to a lack of blinding. The available evidence suggests that acellular substitutes are an effective treatment for diabetic foot ulcer compared to standard wound care alone, but no definitive conclusions can be drawn on acellular skin substitutes benefit over cellular skin substitutes. More large, well-designed clinical trials are needed to evaluate comparative effectiveness and safety of acellular skin substitutes as adjuncts to standard wound care. Hayes concludes:

- C—"For use of acellular skin substitutes as an adjunct to standard wound care (SWC) to treat chronic, uninfected diabetes-associated foot ulcers (DFUs) that have not healed with SWC alone in adults with well-controlled blood glucose and adequate blood flow to the extremities.

  This Rating reflects an overall low-quality body of evidence, which suggests that while acellular skin substitutes appear to be safe and their addition to SWC results in healing of more chronic DFUs than SWC alone in a shorter time frame, questions remain about their effect on the incidence of amputation and on ulcer recurrence due to the limited number of studies on these outcomes. Use of acellular skin substitutes does not appear to present unique or serious safety concerns. Evidence directly comparing different acellular skin substitutes or comparing acellular with cellular skin substitutes is of very low quality, extremely limited, and insufficient to inform whether any 1 product or product type is superior."[25]

- In 2020 (and reviewed in 2023), Hayes conducted a comparative effectiveness review to evaluate skin substitutes for chronic venous leg ulcers in adults.[4] The evidence review identified 8 studies from 10 publications on skin substitutes as adjunct to standard wound care for venous leg ulcers that met the inclusion criteria, 5 RCTs and 3 retrospective observational studies. Hayes categorized studies as follows: one good-quality RCT, 4 fair-quality RCTs, and 3 poor-quality retrospective studies. Primary outcomes measured include complete ulcer closure, time to complete ulcer closure, and time to healing.

  Eight studies (5 RCTs and 3 retrospective studies) reported on incidence of complete ulcer healing. One RCT found a significant increase in complete ulcer healing for application for Talymed once every other week relative to standard wound care (86.4% versus 45%). Two RCTs found that the Epifix group had a higher rate of complete healing compared to standard wound care alone. Another study found no significant difference between skin substitutes (Dermagraft) and standard wound care at 12 and 24 weeks. Two retrospective studies comparing cellular (Apligraf) to acellular (Oasis and Primatrix) skin substitutes found that Apligraf had significantly higher rates of complete healing compared to the acellular substitutes. Two studied compared Apligraf and Theraskin and found conflicting results. One RCT found no significant difference between the skin substitutes on incidence of complete ulcer healing, while a retrospective study found higher rates in the Apligraf group.
  Four studies reported on time to complete ulcer healing. One RCT found no difference in time comparing cellular skin substitutes to standard wound care. Two retrospective studies found quicker healing times in cellular versus acellular skin substitutes and one retrospective study found Apligraf to have quicker healing times than Theraskin. Through this analysis, Hayes concluded that skin substitutes appear to be safe and there is a low-quality body of evidence that suggests skin substitutes may improve healing of chronic venous leg ulcers when added to standard wound care. Hayes gave skin substitutes for venosus ulcer in adults a C rating.

- In 2016, Santema et al. conducted a Cochrane systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers.[26] Following the Cochrane Collaboration methodology, independent reviewers systematically identified relevant literature, assessed quality and extracted data. The outcomes of interest included proportion of ulcers completely healed, time to complete ulcer healing, and incidence of lower limb amputations.

  The authors identified 17 randomized controlled trials as eligible for inclusion, encompassing 1, 655 patients with diabetic foot ulcerations. Of these trials, 13 compared a skin substitute to standard of care and 4 compared two types of skin substitutes. "When including all randomized participants, the proportion of completely healed ulcers ranged between 7.7% and 56.3% in the standard care group and 21.1% and 92.3% in the intervention group. The pooled risk ratio (RR) for complete ulcer healing was 1.55 in favor of the intervention group (95 % CI 1.30 –1.85; RD 0.25, 95 % CI 0.14–0. 37; NNT 4, 95% CI 3–8)."[26] The reporting was very heterogeneous for the outcome of time to complete ulcer healing; therefore, it was not possible to make clinical relevant comparisons. When pooling the studies that evaluated the incidence of lower limb amputations, the authors found a statistically significant lower amputation rate for the skin substitute group at 12 weeks.
  This Cochrane systematic review was of good quality and had several strengths, including:

  1. the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol
  2. contacting authors of selected studies for additional information or data
  3. assessment of heterogeneity, reporting bias, and publication bias
  4. meta-analyses only being conducted when studies were determined to be homogeneous
  5. sensitivity analyses to evaluate the influence of studies with a high risk of bias or high losses to follow-up

  Limitations of this systematic review were the inclusion of studies with a high risk of bias and the potential for publication bias. Ultimately, the authors concluded "(t)his systematic review provides evidence that skin substitutes can, in addition to standard care, increase the likelihood of achieving complete ulcer closure compared with standard care alone in the treatment of diabetic foot ulcers."[26]

Medically Necessary Skin Substitutes

The following evidence tables are intended to succinctly list the peer-reviewed literature which supports medical necessity for the respective products. An evidence review was not performed for products which are included in the systematic reviews described above. Due to the large body of evidence, only the most recent peer-reviewed medical literature is included in the citations.

Breast Reconstruction

Products	Evidence
Allogenic Acellular Dermal Matrix (ADM) products	Allogenic (ADM) products (including both AlloDerm® and FlexHD® Acellular Hydrated Dermis) are established products for breast reconstruction and are supported in the peer-reviewed medical literature.[23,27-32]

Burn Wound

Products	Evidence
Biosynthetic dressing products	The peer-reviewed medical literature supports the use of biosynthetic dressing products (including Biobrane®/Biobrane®-L) as a temporary skin substitute in acute burn wounds.[33-35] In general, these products performed better than the standard of care for wound healing rates, length of hospital stay, and pain.
Cultured epidermal autograft products Epicel	Cultured epidermal autograft products (Epicel) received FDA approval under a Humanitarian Device Exemption (HDE); therefore, this product is exempt from the effectiveness requirements necessary for FDA approval. The evidence review did identify two nonrandomized studies which evaluated Epicel for burn wounds.[36,37] The most recent study (Carsin et al.) found that Epicel provided extensive and permanent burn coverage and improved the survival rate in severely burned patients.
Dermal regeneration and bilayer products	The Integra dermal regeneration and bilayer products (including Integra® Dermal Regeneration Template; Integra® Omnigraft Dermal Regeneration Matrix; Integra® Bilayer Matrix Wound Dressing; Integra® Meshed Bilayer Wound Matrix) are well-established in the peer-reviewed medical literature as safe and effective treatments for burn wounds.[38-44]
Human fibroblast-derived temporary skin substitute	The peer-reviewed medical literature supports human fibroblast-derived temporary skin substitute (such as TransCyte) as a safe and effective treatment for burn wounds.[45-49] Results of these clinical trials indicated that TransCyte promoted faster healing, less scaring, and shorter hospital stays.

Diabetic Foot Ulcer

Products	Evidence
Apligraf®	This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.
Allopatch	This product was included in the Hayes comparative effectiveness review
Amnioband	This product was included in the Hayes comparative effectiveness review
Dermagraft®	This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.
EpiFix® Amniotic Membrane	This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.
Grafix® Core/Grafix® Prime	Recent randomized controlled trials support the efficacy of Grafix products for the treatment of diabetic foot ulcers (DFU).[50,51] Both studies showed that treatment of DFU with Grafix significantly improved healing, reduced DFU- related complications, and shortened healing times. A 2022 Hayes review found consistent evidence from low-quality studies that adjunctive treatment with Grafix may improve healing of DFU.[52]
GraftJacket® Regenerative Tissue Matrix	This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.

– Integra® Dermal Regeneration Template – Integra™ Omnigraft Dermal Regeneration Matrix	The use of Integra products for the treatment of diabetic foot ulcers (DFU) is supported in the peer-reviewed literature by randomized controlled trials (RCT).[53,54] A good-quality RCT by Driver et al. (2015) was conducted at 32 sites and randomized 307 patients to treatment with Integra or standard of care. Patients were treated for 16 weeks or until complete wound closure and followed-up for an additional 12 weeks. The results showed a statistically significant increase in the rate of complete wound closure for Integra patients compared to the standard of care (51% vs. 32%; p=0.001). In addition, patients treated with Integra had increased healing times and less adverse events. A 2021 ECRI review of these bilayer matrix products by Integra had an evidence bar of "somewhat favorable".[55] One RCT and three case series (reporting on 415 patients) showed that products in addition to standard care improves complete healing rates at 16-week follow-up and reduces time to wound healing.
Oasis® Wound Matrix/Oasis® Ultra Tri-Layer Matrix	This product was included in the Hayes comparative effectiveness review described above.
TheraSkin®	This product was included in the Hayes comparative effectiveness review described above.

Venous Status Ulcer

Products	Evidence
Apligraf®	This product was included in the Hayes comparative effectiveness review described above.
EpiFix® Amniotic Membrane	The use of EpiFix for the treatment of venous stasis ulcers is supported in the peer-reviewed literature by randomized controlled trials (RCT).[56,57] Most recently, Bianchi et al. (2017) conducted a multicenter RCT evaluating 109 patients with venous leg ulcers. Patients were recruited from 15 centers around the U.S. and followed-up for 16 weeks. The results indicated that patients receiving EpiFix in conjunction with compression therapy were statistically significantly more likely to experience complete wound healing than patients receiving standard wound care alone (60% vs. 35% at 12 weeks, p=0.0128; 71% vs. 44% at 16 weeks, p=0.0065). The older RCT by Serena et al. (2014) also showed a statistically significant difference in wound closure rates in favor of the Epifix group at 4 weeks follow-up (62% vs. 32%, p=0.005).
Oasis® Wound Matrix	This product was included in the Hayes comparative effectiveness review described above.
TheraSkin®	This product was included in the Hayes comparative effectiveness review described above.

Parotidectomy

- In 2013, Li et al. conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of different types of grafts for the prevention of Frey syndrome after parotidectomy.[58] Independent reviewers systematically identified relevant literature, assessed

quality, and extracted then pooled data. The outcomes of interest were the relative risk of Frey syndrome using skin substitute grafting or muscle flaps (another preventative measure) following parotidectomy.

The authors identified 14 randomized controlled trails encompassing 1,098 participants as eligible for inclusion. All studies had an unclear risk of bias. Although, the results of the meta-analysis indicated that the use of an acellular dermal matrix can reduce the risk of Frey syndrome up to 82%, the muscle flaps can also reduce the risk of Frey syndrome up to 81%. Additionally, there was no statistically significant difference was found between the acellular dermal matrix and muscle flap groups (RR 0.73, 95% CI 0.15 to 3.53, P = .70).

The strengths of this study include the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol, and the assessment of heterogeneity and sensitivity. Limitations are present in the heterogeneity of included studies and the poor quality of the RCTs (heterogenous patient populations, small sample sizes, and short follow-up periods). The authors concluded that "the evidence suggests grafts are effective in preventing Frey syndrome after peridectomy. More randomized clinical trials are needed to confirm our conclusions and prove the safety of the grafts."[58]

- In 2012, Zeng and colleagues conducted a systematic review and meta-analysis to evaluate the AlloDerm skin substitute for the prevention of Frey syndrome after parotidectomy.[59] Independent reviewers identified relevant studies, extracted and pooled data, and assessed quality. The primary outcome of interest was the relative risk reduction in objective and subjective incidence.

  Following systematic review, the authors had identified 5 studies including 409 patients as eligible for inclusion. Results of the meta-analysis showed a relative risk reduction of 85% in the objective incidence and 68% in the subjective incidence of Frey syndrome with AlloDerm implants. There was also a 91% relative risk reduction in salivary fistula. However, there was no statistically significant reduction in the incidence of facial nerve paralysis or seroma/sialocele.
  Strengths of this systematic review include the evaluation of evidence and extraction of data by independent authors following a pre-defined protocol and the inclusion of only randomized controlled trials. Limitations are present in the significant inter-study heterogeneity, the poor quality of the included studies (small sample sizes, short follow-up periods, lack of blinding, lack of intention to treat analysis), and the small number of included studies (possible publication bias). Ultimately, the authors concluded "(t)here is evidence that AlloDerm reduces the incidence of Frey syndrome effectively and safely, and also has the potential to improve facial contour and decrease salivary fistula. However, it is unclear whether AlloDerm implants improve facial contour and decrease other complications. Thus, further controlled evaluative studies incorporating more precise measures are required."[59]

Not Medically Necessary Skin Substitutes

Other skin substitutes (such as those listed in Policy Criteria XIV.) are considered not medically necessary due to at least one of the following:

- There is no peer-reviewed literature to support the safety and/or clinical utility of the product.
- The available peer-reviewed literature is inadequate to establish the products safety and/or clinical utility due to poor quality studies with a high risk of bias. These studies had small and heterogenous

patient populations, lack of randomized controlled design, lack of a control group, and/or short-term follow-up periods.
- The product requires, but has not yet received U.S. Food and Drug Administration (FDA) approval under the 510(k) premarket notification or premarket approval (PMA) process.

Not Medically Necessary Indications for Skin Substitutes

Hernia Repair

Systematic Reviews

- In 2015, Antoniou et al. conducted a systematic review and meta-analysis to estimate the comparative risk of hernia recurrence following primary suture or biologic mesh repair.[60] Independent authors systematically identified relevant literature, extracted data, and evaluated quality. The primary outcomes of interest were short-term and long-term recurrence rates.

  The authors identified 5 studies (2 randomized controlled trials and 3 case-control studies) encompassing 295 patients as eligible for inclusion. "Short-term recurrence rates were 16.6% and 3.5% for suture repair and biologic mesh repair, respectively (OR 3.74, 95 % CI 1.55–8.98, p = 0.003). Long-term recurrence based on data provided by one trial only was 51.3% and 42.4 %, respectively (OR 1.43, 95 % CI 0.56–3.63, p = 0.45). Sensitivity analysis of the two randomized trials at short-term follow up demonstrated no significant difference (OR 2.54, 95 % CI 0.92–7.02, p = 0.07)."[60]

  The strengths of this study include the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol, and the assessment of heterogeneity and sensitivity. Limitations are present in the small number of included studies, leading to possible publication bias, and the poor quality of included studies. The authors concluded, "(b)iologic mesh repair of large hiatal hernias may confer short-term benefits in terms of hernia recurrence; however, the limited available information does not allow us to make conclusions about the long-term efficacy of biologic mesh in this setting. Individual biologic mesh grafts require further clinical assessment."[60]

- In 2013, Slater and colleagues conducted a systematic review to evaluate the effectiveness and safety of biologic grafts for ventral hernia repair.[61] Independent authors systematically identified relevant literature, extracted data, and evaluated quality. The primary outcomes of interest were recurrence, abdominal wall laxity, surgical morbidity, and adverse events.

  The authors identified 25 retrospective studies as eligible for inclusion. A total of 17 studies encompassing 531 patients were included in the recurrence rate outcome analysis. Overall, the recurrence rate was 13.8%. "Postoperative infection (r^2=.325, P =.011) and total surgical morbidity (r^2=.189, P=.038) were revealed as significant explanatory variables for recurrent hernia."[61] Laxity was reported in 10.5% of patients, and all cases occurred with the Alloderm product. The surgical morbidity rate was 46.3% (95% CI, 33.3-59.6), and infection occurred in 15.9% (95% CI, 9.8-23.2) of patients.

  Strengths of this study include the systematic review of evidence and extraction of data by independent authors; however, the methodological quality of this study is limited due to the poor

quality of the included studies (all nonrandomized retrospective studies). The authors concluded that because no randomized trials were available, the efficacy of biologic grafts for ventral hernia repair could not be properly evaluated.

Randomized Controlled Trials (RCTs)

The evidence review did not identify any RCTs evaluating skin substitutes for hernia repair that were not included in the systematic reviews described above.

Nonrandomized Studies

The evidence review identified four additional recent nonrandomized studies evaluating allographic mesh for hernia repair.[62-65] Meaningful conclusions cannot be drawn from the results of these studies due to methodological limitations; including, but not limited to, lack of randomized controlled design, lack of comparison group, small sample sizes, and short-term follow-up period.

Tympanic Membrane Perforation

No systematic reviews, randomized controlled studies, or prospective cohort studies were found on AlloDerm for tympanic membrane perforations. Retrospective studies, summarized below, are considered low quality of evidence due to high risk of bias from study design, small sample sizes, and confounding variables potentially present in analyses.

A 2005 retrospective investigated the efficacy of AlloDerm versus temporalis fascia in repairing perforations in patients who require surgery for chronic otitis media with perforation. The study reviewed records of 50 patients between 1999 and 2004 and found no significant difference in closure rates between the two grafting materials, but healing time was shortened with AlloDerm. Overall perforation closure rate was 92%, with an 84% success rate for AlloDerm and a 97% success rate for native temporalis fascia.[66]

A 2006 retrospective study was conducted to compare lateral graft type 1 tympanoplasty with traditional underlay type 1 tympanoplasty using AlloDerm for tympanic membrane reconstruction in children. The study reviewed 34 records undergoing tympanoplasty between 2004 and 2005 and found that both groups significantly improved post-surgery, with a perforation closures rate of 94% for the lateral graft group and a closure rate of 88% for the underlay group. The authors conclude, "Results suggest that lateral graft type 1 tympanoplasty using AlloDerm® is effective for tympanic membrane reconstruction in children and should be used when temporalis fascia is not available or the extent of the perforation limits its use."[67]

A 2009 retrospective study on AlloDerm in type I tympanoplasty compared AlloDerm (n=25), fascia reconstruction (n=56), and fascia plus cartilage reconstruction (n=33) and found that AlloDerm significantly reduced operative time when controlled for surgeon and choice of approach, and all grafting approaches had similar success rates. Success rates were 88%, 96.7% and 89% in AlloDerm, fascia, and fascia plus cartilage reconstruction, respectively. [68]

Complex Nasal Reconstruction

The evidence review identified 4 nonrandomized trials evaluating acellular human dermal allograft (AlloDerm) for various nasal reconstruction and repair.[69-72] Studies included 2 case series and 2 observational studies that had sample sizes of 12-54 participants. Conclusions cannot be drawn from the results of these studies due to their methodological limitations; including, but not limited to, lack of randomized controlled design, lack of comparison group, small sample sizes, and short-term follow-up period.

Rotator Cuff Tear

In 2017 (archived), the ECRI Institute conducted a clinical comparison review of allografts for repairing rotator cuff tears.[73] The authors identified two studies (1 small retrospective case series and 1 small prospective comparative trial) evaluating the AlloPatch HD and Arthroflex products for this indication. Overall, the evidence was inconclusive because of insufficient data. There was no published peer-reviewed literature that examined how well these products worked compared to the standard of care. The authors concluded by stating that randomized controlled trials comparing rotator cuff tear repair with and without these products, with a minimum of 2-year follow-up, are required to determine if there is an improvement in surgical outcomes.

Repair of Non-Traumatic Surgical Wounds

The evidence related to skin substitutes for the repair of non-traumatic surgical wounds (e.g., Mohs surgery for squamous or basal cell carcinomas) is limited to small case series and nonrandomized studies.[74-83] Due to the poor methodological quality of these studies (lack of randomized design, lack of a control group, small sample sizes, short follow-up period, and lack of statistical analysis), there is insufficient evidence to establish the safety and medical necessity of skin substitutes for this indication. Further studies of good-methodological quality are required to support the effectiveness of skin substitutes for repair of non-traumatic surgical wounds, specifically Mohs surgery for squamous or basal cell carcinomas.

CLINICAL PRACTICE GUIDELINES

National Institute for Health and Care Excellence (NICE)

The 2016 (updated in 2019) evidence-based NICE guideline for the prevention and management of diabetic foot problems recommended, “dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.”[84]

Society for Vascular Surgery/American Venous Forum

The 2014 evidence-based Society for Vascular Surgery/American Venous Forum guideline for the management of venous leg ulcers recommended the following:[85]

- The Committee suggests against split-thickness skin grafting as primary therapy in treatment of venous leg ulcers. [Grade - 2; Level of Evidence - B] The Committee suggests split-thickness skin grafting with continued compression for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4 to 6 weeks. [Grade - 2; Level of Evidence - B]

- The Committee suggests the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) to increase the chances for healing in patients with difficult to heal venous leg ulcers in addition to compression therapy in patients who have failed to show signs of healing after standard therapy for 4 to 6 weeks. [Grade - 2; Level of Evidence - A]
- We recommend serial venous leg ulcer wound measurement and documentation. [BEST PRACTICE]. "Serial VLU wound measurement and documentation is important to determine baseline markers and effect of subsequent treatment measures on healing parameters. Documentation should include number and position of ulcers on the leg. Wound measurements should be made for each VLU, including area, perimeter, and depth, with additional descriptors of wound edge parameters, wound base quality, drainage, and infection."

We suggest reapplication of cellular therapy as long as the venous leg ulcer continues to respond on the basis of wound documentation. [GRADE - 2; LEVEL OF EVIDENCE - C]. "The optimal frequency and timing of reapplication of biologic skin substitutes to VLUs remain controversial with little consensus in published studies…With no comparative dosing studies published to determine clinical or economic outcomes, the frequency of application remains at the discretion of the clinician. Current clinical practice has included application of grafts followed by a period of 1 to 3 weeks of observation to determine effectiveness before reapplication is considered."

EVIDENCE SUMMARY

The evidence supports the efficacy and safety of select skin substitute products for the indications of breast reconstruction, burn wounds, diabetic foot ulcers, and venous stasis ulcers. The National Institute for Health and Care Excellence (NICE) recommends the use of skin substitutes as an adjunct to standard care when treating refractor diabetic foot ulcers. The Society for Vascular Surgery and the American Venous Forum also recommends skin substitutes in patients with refractory venous stasis ulcers.
The evidence is insufficient to establish the efficacy, safety, and medical necessity of several products due to a lack of high-quality peer-reviewed literature or a lack of appropriate regulation. In addition, there is not enough evidence to support the use of skin substitutes for other indications, including hernia repair, repair of rotator cuff tears, repair of non-traumatic surgical wounds (e.g., Mohs surgery), and for the prevention of parotidectomy complications. Further studies of good methodological quality are required to establish the safety, effectiveness, and clinical utility of these products and indications.

BILLING GUIDELINES AND CODING

Codes billed in association with the primary product code may also be denied if the product is not covered per the policy criteria above.

The following products are considered medically necessary and covered when billed for vocal cord paralysis treatment:

For vocal cord paralysis treatment, the following diagnosis codes should be used:

- J38.02 Paralysis of vocal cords and larynx, bilateral
- J38.00 Paralysis of vocal cords and larynx, unspecified
- J38.01 Paralysis of vocal cords and larynx, unilateral

CODES*		
CPT	15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk) (List separately in addition to code for primary procedure)
HCPCS	A2001	Innovamatrix ac, per square centimeter
	A2002	Mirragen advanced wound matrix, per square centimeter
	A2004	Xcellistem, 1mg
	A2005	Microlyte matrix, per square centimeter
	A2006	Novosorb synpath dermal matrix, per square centimeter
	A2007	Restrata, per square centimeter
	A2008	Theragenesis, per square centimeter
	A2009	Symphony, per square centimeter
	A2010	Apis, per square centimeter
	A2011	Supra sdrm, per square centimeter
	A2012	Suprathel, per square centimeter
	A2013	Innovamatrix fs, per square centimeter

	A2014	Omeza collagen matrix, per 100 mg
	A2015	Phoenix wound matrix, per square centimeter
	A2016	Permeaderm b, per square centimeter
	A2017	Permeaderm glove, each
	A2018	Permeaderm c, per square centimeter
	A2019	Kerecis omega3 marigen shield, per square centimeter
	A2020	Ac5 advanced wound system (ac5)
	A2021	Neomatrix, per square centimeter
	A2022	Innovaburn or innovamatrix xl, per square centimeter
	A2023	Innovamatrix pd, 1 mg
	A2024	Resolve matrix, per square centimeter
	A2025	Miro3d, per cubic centimeter
	A4100	Skin substitute, FDA cleared as a device, not otherwise specified
	C1763	Connective tissue, non-human (includes synthetic)
	C1781	Mesh (implantable)
	~~C1849~~	**TERMED 12/31/2022** ~~Skin substitute, synthetic, resorbable, per square centimeter~~
	C1832	Autograft suspension, including cell processing and application, and all system components
	C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (tenoglide tendon protector sheet), per square centimeter
	C9363	Skin substitute, integra meshed bilayer wound matrix, per square centimeter
	C9364	Porcine implant, permacol, per square centimeter
	C9399	Unclassified drugs or biologicals
	Q4100	Skin substitute, not otherwise specified
	Q4101	Apligraf, per square centimeter
	Q4102	Oasis wound matrix, per square centimeter
	Q4103	Oasis burn matrix, per square centimeter
	Q4104	Integra bilayer matrix wound dressing (bmwd), per square centimeter
	Q4105	Integra dermal regeneration template (drt) or integra omnigraft dermal regeneration matrix, per square centimeter
	Q4106	Dermagraft, per square centimeter
	Q4107	Graftjacket, per square centimeter
	Q4108	Integra matrix, per square centimeter
	Q4110	Primatrix, per square centimeter
	Q4111	Gammagraft, per square centimeter
	Q4112	Cymetra, injectable, 1 cc
	Q4113	Graftjacket xpress, injectable, 1 cc
	Q4114	Integra flowable wound matrix, injectable, 1 cc
	Q4115	Alloskin, per square centimeter
	Q4116	Alloderm, per square centimeter
	Q4117	Hyalomatrix, per square centimeter
	Q4118	Acell Matristem micromatrix, 1 mg
	Q4121	Theraskin, per square centimeter
	Q4122	Dermacell, per square centimeter
	Q4124	Oasis ultra tri-layer wound matrix, per square centimeter

	Q4123	Alloskin rt, per square centimeter
	Q4125	Arthroflex, per square centimeter
	Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter
	Q4127	Talymed, per square centimeter
	Q4128	Flex hd, or allopatch hd, per square centimeter
	Q4130	Strattice tm, per square centimeter
	Q4132	Grafix core, per square centimeter
	Q4133	Grafix prime , grafixpl prime, stravix and stravixpl, per square centimeter
	Q4134	Hmatrix, per square centimeter
	Q4135	Mediskin, per square centimeter
	Q4136	Ez-derm, per square centimeter
	Q4137	Amnioexcel or biodexcel, per square centimeter
	Q4138	Biodfence dryflex, per square centimeter
	Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
	Q4140	Biodfence, per square centimeter
	Q4141	Alloskin ac, per square centimeter
	Q4142	Xcm biologic tissue matrix, per square centimeter
	Q4143	Repriza, per square centimeter
	Q4145	Epifix, injectable, 1 mg
	Q4146	Tensix, per square centimeter
	Q4147	Architect, architect px, or architect fx, extracellular matrix, per square centimeter
	Q4148	Neox 1k, per square centimeter
	Q4149	Excellagen, 0.1 cc
	Q4150	Allowrap ds or dry, per square centimeter
	Q4151	Amnioband or guardian, per square centimeter
	Q4152	Dermapure, per square centimeter
	Q4153	Dermavest and plurivest, per square centimeter
	Q4154	Biovance, per square centimeter
	Q4155	Neoxflo or clarixflo, 1 mg
	Q4156	Neox 100 or clarix 100, per square centimeter
	Q4157	Revitalon, per square centimeter
	Q4158	Kerecis omega3, per square centimeter
	Q4159	Affinity, per square centimeter
	Q4160	Nushield, per square centimeter
	Q4161	Bio-connekt wound matrix, per square centimeter
	Q4162	Woundex flow, bioskin flow, 0.5 cc
	Q4163	Woundex, bioskin, per square centimeter
	Q4164	Helicoll, per square centimeter
	Q4165	Keramatrix, per square centimeter
	Q4166	Acell Cytal, per square centimeter
	Q4167	Truskin, per square centimeter
	Q4168	Amnioband, 1 mg
	Q4169	Artacent wound, per square centimeter
	Q4170	Cygnus, per square centimeter
	Q4171	Interfyl, 1 mg

	Q4173	Palingen or palingen xplus, per square centimeter
	Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
	Q4175	Miroderm, per square centimeter
	Q4176	Neopatch, per square centimeter
	Q4177	Floweramnioflo, 0.1 cc
	Q4178	Floweramniopatch, per square centimeter
	Q4179	Flowerderm, per square centimeter
	Q4180	Revita, per square centimeter
	Q4181	Amnio wound, per square centimeter
	Q4182	Transcyte, per square centimeter
	Q4183	Surgigraft, per square centimeter
	Q4184	Cellesta, per square centimeter
	Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
	Q4186	Epifix, per square centimeter
	Q4187	Epicord, per square centimeter
	Q4188	Amnioarmor, per square centimeter
	Q4189	Artacent ac, 1 mg
	Q4190	Artacent ac, per square centimeter
	Q4191	Restorigin, per square centimeter
	Q4192	Restorigin, 1 cc
	Q4193	Coll-e-derm, per square centimeter
	Q4194	Novachor, per square centimeter
	Q4195	Puraply, per square centimeter
	Q4196	Puraply am, per square centimeter
	Q4197	Puraply xt, per square centimeter
	Q4198	Genesis amniotic membrane, per square centimeter
	Q4199	Cygnus matrix, per square centimeter
	Q4200	Skin te, per square centimeter
	Q4201	Matrion, per square centimeter
	Q4202	Keroxx (2.5g/cc), 1cc
	Q4203	Derma-gide, per square centimeter
	Q4204	Xwrap, per square centimeter
	Q4205	Membrane graft or membrane wrap, per square centimeter
	Q4206	Fluid flow or fluid GF, 1 cc
	Q4208	Novafix, per square cenitmeter
	Q4209	Surgraft, per square centimeter
	Q4210	Axolotl graft or axolotl dualgraft, per square centimeter
	Q4211	Amnion bio or Axobiomembrane, per square centimeter
	Q4212	Allogen, per cc
	Q4213	Ascent, 0.5 mg
	Q4214	Cellesta cord, per square centimeter
	Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
	Q4216	Artacent cord, per square centimeter
	Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
	Q4218	Surgicord, per square centimeter

	Q4219	Surgigraft-dual, per square centimeter
	Q4220	BellaCell HD or Surederm, per square centimeter
	Q4221	Amniowrap2, per square centimeter
	Q4222	Progenamatrix, per square centimeter
	Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
	Q4225	Amniobind or dermbind tl, per square centimeter
	Q4226	MyOwn skin, includes harvesting and preparation procedures, per square centimeter
	Q4227	Amniocore, per square centimeter
	~~Q4228~~	~~TERMED 10/1/2021~~ ~~Bionextpatch, per square centimeter~~
	Q4229	Cogenex amniotic membrane, per square centimeter
	Q4230	Cogenex flowable amnion, per 0.5 cc
	Q4231	Corplex p, per cc
	Q4232	Corplex, per square centimeter
	Q4233	Surfactor or nudyn, per 0.5 cc
	Q4234	Xcellerate, per square centimeter
	Q4235	Amniorepair or altiply, per square centimeter
	Q4236	Carepatch, per square centimeter
	Q4237	Cryo-cord, per square centimeter
	Q4238	Derm-maxx, per square centimeter
	Q4239	Amnio-maxx or amnio-maxx lite, per square centimeter
	Q4240	Corecyte, for topical use only, per 0.5 cc
	Q4241	Polycyte, for topical use only, per 0.5 cc
	Q4242	Amniocyte plus, per 0.5 cc
	Q4244	Procenta, per 200 mg
	Q4245	Amniotext, per cc
	Q4246	Coretext or protext, per cc
	Q4247	Amniotext patch, per square centimeter
	Q4248	Dermacyte amniotic membrane allograft, per square centimeter
	Q4249	Amniply, for topical use only, per square centimeter
	Q4250	Amnioamp-mp, per square centimeter
	Q4251	Vim, per square centimeter
	Q4252	Vendaje, per square centimeter
	Q4253	Zenith amniotic membrane, per square centimeter
	Q4254	Novafix dl, per square centimeter
	Q4255	Reguard, for topical use only, per square centimeter
	Q4256	Mlg-complete, per square centimeter
	Q4257	Relese, per square centimeter
	Q4258	Enverse, per square centimeter
	Q4259	Celera dual layer or celera dual membrane, per square centimeter
	Q4260	Signature apatch, per square centimeter
	Q4261	Tag, per square centimeter
	Q4262	Dual layer impax membrane, per square centimeter
	Q4263	Surgraft tl, per square centimeter
	Q4264	Cocoon membrane, per square centimeter

	Q4265	Neostim tl, per square centimeter
	Q4266	Neostim membrane, per square centimeter
	Q4267	Neostim dl, per square centimeter
	Q4268	Surgraft ft, per square centimeter
	Q4269	Surgraft xt, per square centimeter
	Q4270	Complete sl, per square centimeter
	Q4271	Complete ft, per square centimeter
	Q4272	Esano a, per square centimeter
	Q4273	Esano aaa, per square centimeter
	Q4274	Esano ac, per square centimeter
	Q4275	Esano aca, per square centimeter
	Q4276	Orion, per square centimeter
	Q4277	Woundplus membrane or e-graft, per square centimeter
	Q4278	Epieffect, per square centimeter
	Q4279	Vendaje ac, per square centimeter
	Q4280	Xcell amnio matrix, per square centimeter
	Q4281	Barrera SL or barrera DL, per square centimeter
	Q4282	Cygnus Dual, per square centimeter
	Q4283	Biovance tri-layer or biovance 3l, per square centimeter
	Q4284	Dermabind sl, per square centimeter
	Q4285	Nudyn dl or nudyn dl mesh, per square centimeter
	Q4286	Nudyn sl or nudyn slw, per square centimeter
	Q4287	Dermabind dl, per square centimeter
	Q4288	Dermabind ch, per square centimeter
	Q4289	Revoshield + amniotic barrier, per square centimeter
	Q4290	Membrane wrap-hydro, per square centimeter
	Q4291	Lamellas xt, per square centimeter
	Q4292	Lamellas, per square centimeter
	Q4293	Acesso dl, per square centimeter
	Q4294	Amnio quad-core, per square centimeter
	Q4295	Amnio tri-core amniotic, per square centimeter
	Q4296	Rebound matrix, per square centimeter
	Q4297	Emerge matrix, per square centimeter
	Q4298	Amniocore pro, per square centimeter
	Q4299	Amnicore pro+, per square centimeter
	Q4300	Acesso tl, per square centimeter
	Q4301	Activate matrix, per square centimeter
	Q4302	Complete aca, per square centimeter
	Q4303	Complete aa, per square centimeter
	Q4304	Grafix plus, per square centimeter

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.

- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
3/2023	Annual review. Investigational criteria changed to Not Medically Necessary.
4/2023	Interim review. 4/1 code update.
7/2023	Interim review. 7/1 code update.
10/2023	Interim review. 10/1 code update.
1/2024	Q1 2024 code set update
2/2024	Annual review. Update to criterion XII to remove product names.