CLINICAL MEDICAL POLICY	
Policy Name:	Skin Replacement Therapy for Chronic Non healing Wounds in the Outpatient Setting
Policy Number:	MP-032-MD-DE
Responsible Department(s):	Medical Management
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Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 31

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary skin replacement products when used in the treatment of chronic, non-healing wounds.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Autologous/Autografts Skin Grafts – Permanent skin coverings that use skin from other parts of the patient's body.

Autograft – A sample of the patient's own healthy skin, as pinch or mesh grafts, is harvested and placed in the ulcer in split- or full-thickness grafts; alternatively the patient's cells may be grown in a laboratory to form a thin film (cultured keratinocyte autograft, or cultured epidermal autograft), which can take 3 to 4 weeks.

Allograft – Skin or tissue harvested from another human being (e.g., cadaver) used as a temporary skin replacement and must be replaced by either an autograft or the ingrowth of the patient's own skin.

Xenograft – Skin or tissue is harvested from an animal with similar skin structure (usually pigs or cows).

Ankle-Brachial Index (ABI) –This is a numeric value of the ratio of the blood pressure at the ankle to the blood pressure in the upper arm (brachium) by Doppler ultrasound. Compared to the arm, lower blood pressure in the leg is an indication of blocked arteries.

Bio-engineered Skin and Soft Tissues – Tissues that may be derived from human tissue (autologous or allogeneic), non-human tissue (xenographic), synthetic material, or a composite of these materials.

Acellular Products – Skin products that contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin.

Cellular Products – Skin products that contain living cells such as fibroblasts and keratinocytes with a matrix.

Chronic Wound – A wound that does not respond to standard wound treatment for at least a 30-day period during organized comprehensive therapy.

Failed Response – An ulcer or skin deficit that has failed to respond to documented appropriate wound care measures, has increased in size or depth, or has not changed in baseline size or depth, and has no indication that improvement is likely.

Standard Treatment of Chronic Lower Extremity Ulcers – Therapies that primarily include infection and edema control, mechanical off-loading, mechanical compression or limb elevation, debridement of necrotic or infected tissue, and management of concomitant medical issues (e.g., blood glucose control, tobacco use).

Lower Extremity – Anatomically defined as the hip, thigh, leg, ankle, and foot.

PROCEDURES

This medical policy addresses the use of skin replacement products for the treatment of chronic non-healing wounds. The goal of this treatment is to provide temporary wound coverage, complete wound closure, reduced time to heal, lessen pain, minimize post-operative contracture, and improve overall quality of health.

The following general information is required for all covered indications:

- The ordering provider must be a physician licensed by the state with full scope of practice for the treatment of the systemic disease process that is responsible for causing the chronic non-healing wound; AND
- In the situation when the performing provider is NOT the physician caring for the systemic disease, the performing provider must document in the medical record that he/she is aware of the systemic condition and notates the identity of the physician who is responsible for care related to the condition; AND
- The patient's wound has a failure of response (an ulcer or skin deficit that has failed to respond to clearly documented appropriate wound care, has a wound that has increased in size or depth, or has not changed in baseline size or depth, and there is no indication that improvement is expected); AND
- There must be evidence of adequate arterial blood supply (e.g., ankle-brachial index of 0.65 or greater in the affected limb; AND
- There must be an evaluation and provision for adequate nutritional status, including pre-albumin and albumin levels.

1. Chronic Non-Healing Wounds

   In addition to the general information above, the following wound-specific medical necessity criteria must be met:

   A. Diabetic Foot Ulcers (DFU)

      Indication(s):

      1) Presence of a neuropathic diabetic foot ulcer of greater than four weeks which has failed to respond to documented conservative wound care measures such as surgical debridement, complete off-loading, and standard dressing changes; AND
      2) There must be documentation of patient compliance with all conservative wound care measures; AND
      3) The foot ulcer must extend through the dermis but without tendon, muscle, joint capsule, or bone exposure; AND
      4) The diabetes is well managed, and the HbA1C is within an acceptable range; AND
      5) The diabetic foot ulcer is free of infection; AND
      6) Wound must have adequate circulation and presence of acceptable peripheral pulses or as evidenced by ankle-brachial index (ABI) of 0.65 or greater in the limb being treated. An index of greater than 0.45 is needed to heal.

      Product(s):

      - Apligraf ®; OR
      - AlloPatch Pliable®; OR
      - AlloDerm; OR
      - Biovance; OR
      - Dermagraft; OR
      - DermaPure; OR

- Helicoll; OR
- Integra® Bilayer Wound Matrix; OR
- Integra Omnigraft dermal regeneration matrix®; OR
- Kermatrix; OR
- TheraSkin; OR
- Oasis™ wound matrix; OR
- Epifix; OR
- Graftjacket Regenerative Tissue Matrix (RTM); OR
- Grafix; OR
- TheraSkin®

B. Venous Leg Ulcers (VLU)
Indication(s):
1) The presence of a venous stasis ulcer which has not responded to documented appropriate therapy for greater than four weeks. These therapies would include the use of compression therapy using multilayer dressings or compression stockings with greater than 20 mmHG pressure or pneumatic compression; AND
2) There must be documentation that the patient has been compliant with wound care measures.

Product(s):
- Apligraf ®; OR
- AlloDerm; OR
- Biovance; OR
- DermaPure; OR
- Integra® Bilayer Wound Matrix; OR
- Oasis™ Wound Matrix; OR
- TheraSkin®

2. Documentation requirements for all wound types
   A. Medical record documentation includes measurements of the initial ulcer, measurements at the completion of at least four weeks of appropriate wound care, and measurements immediately prior to skin replacement product and with each subsequent placement of skin products;
   B. Medical record documentation that specifically states the reason that the wound has failed to heal with standard wound care;
   C. Medical record documentation that demonstrates that the medical policy criteria have been met, along with appropriate diagnoses and response to treatment(s);
   D. Medical record has clear descriptions of the wound(s) relative to the location, stage, size duration, and presence or lack of infection. There must be a wound description pre- and post-treatment with each skin replacement application.
   E. Documentation of the amount of skin replacement product used and amount wasted.
   F. Timing, frequency, and number of reapplications of bioengineered skin substitutes should be appropriate for the material used and clinical condition of the patient.
   In a course of treatment, repeat application of skin substitutes/replacements are not indicated when prior application were unsuccessful.

3. Contraindications
   Presence of any of the following:

A. Edema, venous hypertension, or lymphedema
B. Active cellulitis, osteomyelitis, foreign body, or malignant process
C. Tunneling and tracts, eschar and necrotic material

4. Length of Coverage
   A single application of skin replacement products is usually all that is necessary in order to effect wound healing in wounds that are likely to be improved by this therapy. The use of more than two applications for the same ulcer within six months is considered not medically necessary. Requests for additional skin replacement applications will be reviewed on a case-by-case basis with supporting medical record documentation.

   Retreatment within one year following successful initial treatment (up to two applications) is not considered medically necessary.

5. When services are not covered
   A. For conditions other than those listed above, scientific evidence has not been established.
   B. Services are not covered for the use of a skin replacement product for indications not approved by the FDA or in accordance with the manufacturer's package guidelines.
   C. Services are not covered for the use of Autologous Platelet Rich Plasma (PRP) and are considered experimental/investigation and therefore considered not medically necessary.
   D. Simultaneous use of more than one product for the episode of the wound is not covered.

6. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

7. Place of Service
   The place of service for the placement of skin replacement products can be outpatient or the provider office.

GOVERNING BODIES APPROVAL

Based on the skin substitute's composition and origin, the U.S. Food and Drug Administration (FDA) regulates skin substitutes under one of the following categories:

A. Human- and human/animal-derived products regulated through the premarket approval (PMA) process
B. Animal-derived products and synthetic products regulated through the 510(k) process
C. Human-derived products regulated as human cells, tissue, and cellular and tissue-based products (HCT/Ps)
D. Human- and human/animal-derived products regulated as a Humanitarian Use Device (HUD) obtained through a Humanitarian Device Exemption (HDE)

Premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or that present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, the FDA has determined that general and special controls alone are insufficient to ensure the safety and effectiveness

of Class III devices. Therefore, these devices require a premarket approval application in order to obtain marketing clearance.

PMA is the most stringent type of device marketing application required by the FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by the FDA that there is sufficient valid scientific evidence to ensure that the device is safe and effective for its intended use(s).

FDA PREMARKETING NOTIFICATION (510[k])
A Premarketing Notification (510[k]) is a process in which applicants must demonstrate that the device to be marketed (e.g., a Class II device) is "substantially equivalent" to a pre-existing legally marketed device (predicate) in terms of safety and effectiveness. The predicate must have been approved either via PMA or 510(k). This process is usually used when manufacturers make small changes to a previously approved device that are thought to improve effectiveness without compromising safety, thus allowing for expedited approval without costly and lengthy scientific studies confirming safety and effectiveness.

HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/Ps)
Cells and tissues taken from human donors and transplanted to a recipient are regulated under Public Health Services (PHS) 361 [21 CFR 1270 & 1271]. This regulation describes the rules concerning the use of HCT/Ps for human medical purposes. The final rule, 21 CFR Part 1271, became effective on April 4, 2001, for human tissues intended for transplantation that are regulated under section 361 of the PHS Act and 21 CFR Part 1270. HCT/Ps are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Establishments producing HCT/Ps must register with the FDA and list their HCT/Ps. HCT/Ps establishments are not required to demonstrate the safety or effectiveness of their products, and the FDA does not evaluate the safety or effectiveness of these products.

HUMANITARIAN DEVICE EXEMPTION (HDE)
In rare instances, certain medical devices intended to be used for humanitarian purposes are evaluated by the FDA through the Humanitarian Device Exemption (HDE) process. A device approved in this manner is designated as a Humanitarian Use Device (HUD). A HUD designation permits the use of certain medical devices when there is no comparable device available to treat or diagnose a disease or condition affecting fewer than 4,000 individuals annually. Because clinical investigation demonstrating the device's efficacy is not feasible (given the low prevalence of the disease in the population), an HDE grants manufacturers an exemption to the usual premarket approval process and allows marketing of the device only for the FDA-labeled HDE indication(s).

Under FDA requirements, an HUD may only be used after institutional review board (IRB) approval has been obtained for the use of the device in accordance with the FDA-labeled indication(s) under the HDE.

Platelet Rich Plasma (PRP)
FDA
The injection of PRP is a procedure and therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as part of this procedure may be subject to FDA regulation.

Centers for Medicare and Medicaid Services (CMS)

Effective August 2, 2012, upon reconsideration, CMS determined that platelet rich plasma—an autologous blood-derived product—would be covered only for the treatment of chronic non-healing diabetic, venous, and/or pressure wounds and only when the patient is enrolled in a clinical trial that addresses certain questions when the clinical trial uses validated and reliable methods of evaluation. Any clinical study undertaken pursuant to the National Coverage Determination (NCD) needed to be approved no later than August 2, 2014. If there were no approved clinical studies on or before August 2, 2014, this Coverage with Evidence Development (CED) would have expired. Any clinical study approved must adhere to the timeframe designated in the approved clinical study protocol. Medicare has no other National Coverage Determination (NCD) for PRP. No updates to this position were identified at the time of this medical policy development.

There are no Local Coverage Determinations (LCD) identified.

CODING REQUIREMENTS

Procedure Codes

CPT Codes	Description
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq. cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq. cm (list separately in addition to code for primary procedure
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq. cm, or each additional 1% of body area of infants and children, or part thereof. (list separately in addition to code for primary procedure)
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq. cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq. cm to 75 sq. cm (list separately in addition to code for primary procedure)
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
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 of 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 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 up to 100 sq. cm; first 100 sq. cm wound surface area, or 1% of body 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 up 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 (e.g., acellular dermal matrix) for soft tissue reinforcement (i.e., breast trunk). (list separately in addition to code for primary procedure)
HCPCS Codes	**Description**
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per sq. cm
Q4102	Oasis wound matrix, per sq. cm (Covered)
Q4104	Integra bilayer matrix wound dressing (BMWD), per sq. cm
Q4105	Integra dermal regeneration template (DRT), per sq. cm (Covered)
Q4106	Dermagraft, per sq. cm (Covered)
Q4107	GRAFTJACKET, per sq. cm (Covered)
Q4108	Integra matrix, per sq. cm
Q4114	Integra flowable wound matrix, injectable, 1 cc
Q4116	AlloDerm, per sq. cm
Q4121	TheraSkin, per sq. cm (Covered)
Q4128	FlexHD, Acellular Hydrated Dermis
Q4131	Epifix, per sq. cm (Covered)
Q4132	Grafix core, per sq. cm (Covered)
Q4133	Grafix prime, per sq. cm
Q4152	Dermapure, per sq. cm
Q4154	Biovance, per sq. cm
Q4164	Helicoll, per sq. cm
Q4165	Keramatrix, per sq. cm

*= TAG Decision

Non-covered Procedure Codes
All requests for the codes listed below require medical director approval

HCPCS Codes	Description
Q4111	GammaGraft, per sq. cm
Q4110	PriMatrix, per sq. cm
Q4112	Cymetra, injectable, 1cc
Q4113	GRAFT JACKET XPRESS, injectable, 1cc
Q4115	AlloSkin, per sq. cm

Q4117	HYALOMATRIX, per sq. cm
Q4118	MatriStem micromatrix, 1 mg
Q4122	Dermacell, per sq. cm
Q4123	AlloSkin RT, per sq. cm
Q4124	OASIS ultra tri-layer wound matrix, per sq. cm
Q4125	Arthroflex, per sq. cm
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per sq. cm
Q4127	Talymed, per sq. cm
Q4134	hMatrix, per sq. cm
Q4135	Mediskin, per sq. cm
Q4136	Ez-derm, per sq. cm
Q4137	Amnioexcel or biodexcel, per sq. cm
Q4138	Biodfence Dryflex, per sq. cm
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	Biodfence, per sq. cm
Q4141	AlloSkin AC, per sq. cm
Q4142	XMC Biologic tissue matrix, per sq. cm
Q4143	Repriza, per sq. cm
Q4145	Epifix, injectable, 1 mg
Q4146	TenSIX, per sq. cm
Q4147	Architect, architect PX, or architect FX, extracellular matrix, per sq. cm
Q4148	Neox 1k, per sq. cm
Q4149	Excellagen, 0.1 cc
Q4150	AlloWrap DS or dry, per sq. cm
Q4151	Amnioband or guardian, per sq. cm
Q4153	Dermavest and plurivest, per sq. cm
Q4155	Neoxflo or clarixflo, 1mg
Q4156	Neox 100, per sq. cm
Q4157	Revitalon, per sq. cm
Q4158	MariGen, per sq. cm
Q4159	Affinity, per sq. cm
Q4160	Nushield, per sq. cm
Q4161	Bio-ConneKt wound matrix, per sq. cm
Q4162	Amniopro flow, bioskin flow, biorenew flow, woundex flow, amniogen-a, amniogen-c, 0.5 cc
Q4163	Amniopro, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per sq. cm
0232T	Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
P9020	Platelet rich plasma, each unit
P9022	Red blood cells, washed, each unit
S9055	Procuren or other growth factor preparation to promote wound healing

*= TAG Decision

Diagnosis Codes

ICD-10 Codes	Description
E08.621	Diabetes mellitus due to underlying condition with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]
E10.621	Type 1 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]
E11.621	Type 2 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]
E13.621	Other specified diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]
E13.622	Other specified diabetes mellitus with other skin ulcer
I70.231	Atherosclerosis of native arteries of right leg with ulceration of thigh
I70.232	Atherosclerosis of native arteries of right leg with ulceration of calf
I70.233	Atherosclerosis of native arteries of right leg with ulceration of ankle
I70.234	Atherosclerosis of native arteries of right leg with ulceration of heel and midfoot
I70.235	Atherosclerosis of native arteries of right leg with ulceration of other part of foot
I70.238	Atherosclerosis of native arteries of right leg with ulceration of other part of lower right leg
I70.241	Atherosclerosis of native arteries of left leg with ulceration of thigh
I70.242	Atherosclerosis of native arteries of left leg with ulceration of calf
I70.243	Atherosclerosis of native arteries of left leg with ulceration of ankle
I70.244	Atherosclerosis of native arteries of left leg with ulceration of heel and midfoot
I70.245	Atherosclerosis of native arteries of left leg with ulceration of other part of foot
I70.248	Atherosclerosis of native arteries of left leg with ulceration of other part of lower left leg
I70.291	Other atherosclerosis of native arteries of extremities, right leg
I70.292	Other atherosclerosis of native arteries of extremities, left leg
I70.293	Other atherosclerosis of native arteries of extremities, bilateral legs
I70.331	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of thigh
I70.332	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of calf
I70.333	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of ankle
I70.334	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of heel and midfoot
I70.335	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of other part of foot
I70.338	Atherosclerosis of unspecified type of bypass graft(s) of the right leg with ulceration of other part of lower leg
I70.341	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of thigh
I70.342	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of calf
I70.343	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of ankle
I70.344	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of heel and midfoot

I70.345	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of other part of foot
I70.348	Atherosclerosis of unspecified type of bypass graft(s) of the left leg with ulceration of other part of lower leg
I83.011	Varicose veins of right lower extremity with ulcer of thigh
I83.012	Varicose veins of right lower extremity with ulcer of calf
I83.013	Varicose veins of right lower extremity with ulcer of ankle
I83.014	Varicose veins of right lower extremity with ulcer of heel and midfoot
I83.015	Varicose veins of right lower extremity with ulcer other part of foot
I83.018	Varicose veins of right lower extremity with ulcer other part of lower leg
I83.021	Varicose veins of left lower extremity with ulcer of thigh
I83.022	Varicose veins of left lower extremity with ulcer of calf
I83.023	Varicose veins of left lower extremity with ulcer of ankle
I83.024	Varicose veins of left lower extremity with ulcer of heel and midfoot
I83.025	Varicose veins of left lower extremity with ulcer other part of foot
I83.028	Varicose veins of left lower extremity with ulcer other part of lower leg
I83.211	Varicose veins of right lower extremity with both ulcer of thigh and inflammation
I83.212	Varicose veins of right lower extremity with both ulcer of calf and inflammation
I83.213	Varicose veins of right lower extremity with both ulcer of ankle and inflammation
I83.214	Varicose veins of right lower extremity with both ulcer of heel and midfoot and inflammation
I83.215	Varicose veins of right lower extremity with both ulcer other part of foot and inflammation
I83.218	Varicose veins of right lower extremity with both ulcer of other part of lower extremity and inflammation
I83.221	Varicose veins of left lower extremity with both ulcer of thigh and inflammation
I83.222	Varicose veins of left lower extremity with both ulcer of calf and inflammation
I83.223	Varicose veins of left lower extremity with both ulcer of ankle and inflammation
I83.224	Varicose veins of left lower extremity with both ulcer of heel and midfoot and inflammation
I83.225	Varicose veins of left lower extremity with both ulcer other part of foot and inflammation
I83.228	Varicose veins of left lower extremity with both ulcer of other part of lower extremity and inflammation
I87.011	Post thrombotic syndrome with ulcer of right lower extremity
I87.012	Post thrombotic syndrome with ulcer of left lower extremity
I87.013	Post thrombotic syndrome with ulcer of bilateral lower extremity
I87.031	Post thrombotic syndrome with ulcer and inflammation of right lower extremity
I87.032	Post thrombotic syndrome with ulcer and inflammation of left lower extremity
I87.033	Post thrombotic syndrome with ulcer and inflammation of bilateral lower extremity
I87.311	Chronic venous hypertension (idiopathic) with ulcer of right lower extremity
I87.312	Chronic venous hypertension (idiopathic) with ulcer of left lower extremity
I87.313	Chronic venous hypertension (idiopathic) with ulcer of bilateral lower extremity
I87.331	Chronic venous hypertension (idiopathic) with ulcer and inflammation of right lower extremity
I87.332	Chronic venous hypertension (idiopathic) with ulcer and inflammation of left lower extremity
I87.333	Chronic venous hypertension (idiopathic) with ulcer and inflammation of bilateral lower extremity
L89.152	Pressure ulcer of sacral region, stage 2

L89.153	Pressure ulcer of sacral region, stage 3
L89.154	Pressure ulcer of sacral region, stage 4
L89.212	Pressure ulcer of right hip, stage 2
L89.213	Pressure ulcer of right hip, stage 3
L89.214	Pressure ulcer of right hip, stage 4
L89.222	Pressure ulcer of left hip, stage 2
L89.223	Pressure ulcer of left hip, stage 3
L89.224	Pressure ulcer of left hip, stage 4
L89.312	Pressure ulcer of right buttock, stage 2
L89.313	Pressure ulcer of right buttock, stage 3
L89.314	Pressure ulcer of right buttock, stage 4
L89.322	Pressure ulcer of left buttock, stage 2
L89.323	Pressure ulcer of left buttock, stage 3
L89.324	Pressure ulcer of left buttock, stage 4
L89.42	Pressure ulcer of contiguous site of back, buttock and hip, stage 2
L89.43	Pressure ulcer of contiguous site of back, buttock and hip, stage 3
L89.44	Pressure ulcer of contiguous site of back, buttock and hip, stage 4
L89.512	Pressure ulcer of right ankle, stage 2
L89.513	Pressure ulcer of right ankle, stage 3
L89.514	Pressure ulcer of right ankle, stage 4
L89.522	Pressure ulcer of left ankle, stage 2
L89.523	Pressure ulcer of left ankle, stage 3
L89.524	Pressure ulcer of left ankle, stage 4
L89.612	Pressure ulcer of right heel, stage 2
L89.613	Pressure ulcer of right heel, stage 3
L89.614	Pressure ulcer of right heel, stage 4
L89.622	Pressure ulcer of left heel, stage 2
L89.623	Pressure ulcer of left heel, stage 3
L89.624	Pressure ulcer of left heel, stage 4
L89.892	Pressure ulcer of other site, stage 2
L89.893	Pressure ulcer of other site, stage 3
L89.894	Pressure ulcer of other site, stage 4
L97.111	Non-pressure chronic ulcer of right thigh limited to breakdown of skin
L97.112	Non-pressure chronic ulcer of right thigh with fat layer exposed
L97.113	Non-pressure chronic ulcer of right thigh with necrosis of muscle
L97.114	Non-pressure chronic ulcer of right thigh with necrosis of bone
L97.121	Non-pressure chronic ulcer of left thigh limited to breakdown of skin
L97.122	Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.123	Non-pressure chronic ulcer of left thigh with necrosis of muscle
L97.124	Non-pressure chronic ulcer of left thigh with necrosis of bone
L97.211	Non-pressure chronic ulcer of right calf limited to breakdown of skin
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.213	Non-pressure chronic ulcer of right calf with necrosis of muscle
L97.214	Non-pressure chronic ulcer of right calf with necrosis of bone
L97.221	Non-pressure chronic ulcer of left calf limited to breakdown of skin
L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.223	Non-pressure chronic ulcer of left calf with necrosis of muscle

L97.224	Non-pressure chronic ulcer of left calf with necrosis of bone
L97.311	Non-pressure chronic ulcer of right ankle limited to breakdown of skin
L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.313	Non-pressure chronic ulcer of right ankle with necrosis of muscle
L97.314	Non-pressure chronic ulcer of right ankle with necrosis of bone
L97.321	Non-pressure chronic ulcer of left ankle limited to breakdown of skin
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.323	Non-pressure chronic ulcer of left ankle with necrosis of muscle
L97.324	Non-pressure chronic ulcer of left ankle with necrosis of bone
L97.411	Non-pressure chronic ulcer of right heel and midfoot limited to breakdown of skin
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.413	Non-pressure chronic ulcer of right heel and midfoot with necrosis of muscle
L97.414	Non-pressure chronic ulcer of right heel and midfoot with necrosis of bone
L97.421	Non-pressure chronic ulcer of left heel and midfoot limited to breakdown of skin
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.423	Non-pressure chronic ulcer of left heel and midfoot with necrosis of muscle
L97.424	Non-pressure chronic ulcer of left heel and midfoot with necrosis of bone
L97.511	Non-pressure chronic ulcer of other part of right foot limited to breakdown of skin
L97.512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.513	Non-pressure chronic ulcer of other part of right foot with necrosis of muscle
L97.514	Non-pressure chronic ulcer of other part of right foot with necrosis of bone
L97.521	Non-pressure chronic ulcer of other part of left foot limited to breakdown of skin
L97.522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.523	Non-pressure chronic ulcer of other part of left foot with necrosis of muscle
L97.524	Non-pressure chronic ulcer of other part of left foot with necrosis of bone
L97.811	Non-pressure chronic ulcer of other part of right lower leg limited to breakdown of skin
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.813	Non-pressure chronic ulcer of other part of right lower leg with necrosis of muscle
L97.814	Non-pressure chronic ulcer of other part of right lower leg with necrosis of bone
L97.821	Non-pressure chronic ulcer of other part of left lower leg limited to breakdown of skin
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97.823	Non-pressure chronic ulcer of other part of left lower leg with necrosis of muscle
L97.824	Non-pressure chronic ulcer of other part of left lower leg with necrosis of bone
L97.912	Non-pressure chronic ulcer of unspecified part of right lower leg with fat layer exposed
L97.913	Non-pressure chronic ulcer of unspecified part of right lower leg with necrosis of muscle
L97.914	Non-pressure chronic ulcer of unspecified part of right lower leg with necrosis of bone
L97.922	Non-pressure chronic ulcer of unspecified part of left lower leg with fat layer exposed
L97.923	Non-pressure chronic ulcer of unspecified part of left lower leg with necrosis of muscle
L97.924	Non-pressure chronic ulcer of unspecified part of left lower leg with necrosis of bone

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Chronic wounds of the lower extremity are known to be a condition associated with high prevalence, high cost, and poor clinical outcome. Wounds become chronic when they are unresponsive to initial therapy or persistent in the face of appropriate care. The most common types of chronic wounds of the lower extremity are described by their etiology:

- Vascular (e.g., arterial, venous, or mixed ulcers)
- Pressure ulcers
- Neuropathic (e.g., diabetic ulcers)

Skin grafting has evolved from the initial autograft and allograft preparations to biosynthetic and tissue engineered human skin equivalents. There are a large number of potential applications for these products, and one large category is non-healing wounds. Non-healing wounds encompass diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. These types of wounds are known to heal inadequately with standard wound care, leading to prolonged morbidity and increased risk of mortality.

Numerous clinical trials have been published for the majority of commercially available skin replacement products for several medical conditions including non-healing wounds, pressure ulcer, inflammatory ulcers, and burns. In addition, there are ongoing and unpublished trials.

In 2015, the United Kingddom's National Institute for Health and Care Excellence (NICE) published clinical guidelines on the prevention and management of diabetic foot problems. NICE recommends that clinicians consider 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.

Autologous platelet-derived growth factors are referred to as platelet rich plasma (PRP), autologous platelet gel, or platelet releasate, and several PRP preparations available today that are FDA approved. There are PRP preparations intended to be used to mix with bone graft materials in order to enhance bone grafting properties in orthopedic practices. There are two preparations that can be prepared at the bedside for immediate application (i.e., AutoGel and SafeBlood), specifically for wound healing. Procuren® (Cytomedix, Inc.) was another product used for chronic wound healing, however, it is no longer manufactured or commercially available.

Platelet-derived growth factor has been suggested for adjunctive use in the management of chronic non-healing wounds. It is not clearly understood how PRP works, but some practitioners speculate that if the acute healing pathways can be activated, the body can be induced to repair damage. Therefore, an injection into the injury site is thought to stimulate an acute injury and may possibly induce an acute healing process.

Several agencies have concluded that the effectiveness of growth factors for this condition have not been adequately established to warrant recommendation for use (AHRQ, 2011) (CMS, 2013). The available studies have mixed results with some trials reporting improvement with PRP and other trials reporting improvement. Additional studies are needed in order to truly resolve these issues.

In 2012, a Cochrane analysis was completed to address autologous PRP used for healing chronic wounds. There were nine eligible random controlled trials (RCT) with a total of 325 participants, and 44% were women. Four RCTs recruited patients with mixed chronic wounds, three RCTs recruited patients for venous leg ulcers and two trials used patients with diabetic foot ulcers. The median length of treatment was 12 weeks. The authors reported that there were no statistically significant differences in groups treated with PRP compared to the groups that were not treated with PRP. In conclusion, there is no

evidence to suggest that autologous PRP is of value for treating chronic wounds, and well-designed, adequately powered clinical trials are needed.

Reference List of Skin Replacement Products

The table below lists skin substitutes, which are represented by a specific HCPCS code, and their approved indications. This list does not include all FDA-approved/regulated skin substitutes. This list does not imply coverage for all products. Please refer to the 'Covered Products' section of the policy for details on specific products.

Skin Substitute	Approved Indication(s)
Medically Necessary:	
Apligraf	Apligraf received premarket FDA approval in 1998 for the treatment of venous leg ulcers (VLU) and in 2001 for the treatment of diabetic foot ulcers. Clinical trials for Apligraf has proven to be effective when used for treatment of VLUs and diabetic foot ulcers (Novartis, 2002). There is not sufficient data to use Apligraf in the treatment of pressure sores, dermatological survey wounds and burns (Novartis, 2002).
Alloderm®	AlloDerm has been widely used in several applications for many years. There is an injectable form of AlloDerm marketed as Cymetra, basically a micronized form. AlloDerm is used as a dermal substitute in deep partial- and full-thickness burn wounds, facilitating subsequent autologous split-thickness skin graft take.
AlloPatch®	Allopatch HD (Conmed, Utica, NY) is an extracellular matrix (ECM) scaffold derived from human allograft skin for tendon augmentation. The Musculoskeletal Transplant Foundation (MTF), which acquires and processes the tissue, is registered with the FDA (Conmed, 2017).
Dermagraft	Indicated for use in the treatment of full-thickness diabetic foot ulcers, which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure. Dermagraft was FDA-approved through the PMA process in 2001 for the treatment of diabetic foot ulcers.
Graftjacket Tissue Matrix	Graftjacket tissue matrix is a wound care product derived from cadaveric skin, which undergoes a process that removes the epidermis and dermal cells. Graftjacket tissue matrix is an acellular regenerative tissue matrix that is designed to provide a scaffold for wound repair. Graftjacket tissue matrix is indicated for full-thickness diabetic foot ulcers greater than three week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.
TheraSkin®	A biologically active, cryopreserved human skin allograft with both epidermis and dermis layers. Similar to living skin equivalent (LSE) and provides a supply of living cells, fibroblasts and keratinocytes and a fully developed extracellular matrix (Snyder, et al., 2012). TheraSkin is regulated by the FDA as an HCT/P (human cells, tissues,

Skin Substitute	Approved Indication(s)
	and cellular and tissue-based products) under 21 CFR part 1270/1271 and section 361 of the Public Health Service Act. TheraSkin is indicated for nonhealing or chronic wounds, pressure ulcers diabetic foot ulcers, venous stasis ulcers and burns.
Integra Bilayer Matrix Wound Dressing (BMWD)	An advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone layer). Integra was cleared for marketing under the 510(k) process in August 2002 and is indicated "for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. This device is intended for one-time use."
Integra® Dermal Regeneration Template (IDRT) and Integra Omnigraft Dermal Regeneration Template:	Omnigraft Dermal Regeneration Matrix (Omnigraft) is an advanced wound care device, comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) layer. In January 2016, the FDA approved the Integra Dermal Regeneration Template (Omnigraft Dermal Regeneration Template) for certain diabetic foot ulcers that last for longer than 6 weeks and do not involve exposure of the joint capsule, tendon or bone, when used in conjunction with standard diabetic ulcer care. The approval was based upon the clinical results of a multi-center, randomized, controlled clinical trial (the Foot Ulcer New Dermal Replacement Study (FOUNDER) Study) (Driver et al, 2015).
Oasis® (Wound Matrix, Ultra tri-layer wound matrix)	A porcine-derived decellularized intestinal mucosa matrix, intended for the management of pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undetermined wounds, surgical wounds, trauma wounds, and draining wounds. Oasis is not indicated for the use in 3rd degree burns.
Biovance	Biovance is a is an amniotic membrane allograft derived from the placenta of a healthy, full-term human pregnancy, intended for the treatment of acute and chronic wounds including burns, diabetic ulcer, pressure ulcers and surgical wounds. Smiell et al. (2015) reported a multicenter registry study of Biovance d-HAM for the treatment of various wound types, including diabetic foot wounds, pressure ulcers, and venous ulcers. The study showed effectiveness of d-HAM in a real-world setting.
DermaPure	DermaPure is a single layer decellularized dermal allograft derived from split thickness grafts harvested from human cadaver tissue donors, DermaPure is used for the treatment of acute and chronic wounds such as diabetic foot ulcers, venous stasis ulcers, and additional wounds that are refractory to more conservative care (CMS, 2014).

Skin Substitute	Approved Indication(s)
	In a 2017 analysis, Kimmel and Gittleman evaluated the use of DermaPure, a decellularized human skin allograft, in the treatment of a variety of challenging wounds. This retrospective observational analysis reviewed a total of 37 patients from 29 different wound clinics. Each patient received one application of DermaPure which was followed until complete closure. A statistical analysis was performed with the end point being complete healing. All wounds on average had a duration of 56 weeks and healed in an average time of 10 weeks. Individual wound categories included diabetic foot ulcers, which healed in 8 weeks; venous leg ulcers, which healed in 11 weeks; and surgical/traumatic wounds, which healed in 11 weeks.
DermaSpan Acellular Dermal Matrix	DermaSpan (Zimmer Biomet® Sports Medicine) is an acellular dermal matrix derived from human allograft tissue. It is intended for use in various practices, including orthopedics, plastic surgery, and general surgery, for repair and replacement of damaged or inadequate skin tissue (wound coverage). Intended use is for the repair or replacement of damaged or inadequate integument tissue (wound coverage).
EpiFix	EpiFix amniotic membrane allograft (MiMedx Group, Inc., Kennesaw, GA) is a biologic human amniotic membrane processed through Surgical Biologic's proprietary Purion® process, which combines cleaning, dehydration and sterilization to produce a safe, technically sterilized tissue allowing for storage at room temperature. Used in the treatment of partial and full-thickness wounds including, but not limited to: diabetic foot ulcers, venous leg ulcers, arterial ulcers, pressure ulcers, and inflammatory ulcers. In a multi-center RCT, Bianchi and colleagues (2018) evaluated the efficacy of EpiFix allograft as an adjunct to multi-layer compression therapy for the treatment of non-healing full-thickness venous leg ulcers. The authors stated that these results may not be generalized to other amniotic membrane products seeing that scientific papers have been published describing differences among the products. They noted that it must also be recognized that all patients received a high level of care in a wound care center. For ethical reasons, per study protocol, patients receiving standard care were allowed to exit the study and receive advanced wound care treatments if their wound did not reduce by a minimum of 40 % within 8 weeks of study enrollment.
Helicoll	Helicoll (MCT Medical Solutions LLC) is a semi occlusive, self-adhering collagen sheet used for wound treatments, second degree burns, and chronic ulcers. This biodegradable skin substitute is made from animal tissues. Dhanraj (2015) conducted a prospective randomized controlled study to compare Helicoll, a type I pure collagen dressing, to OpSite dressing and to Scarlet Red dressing in the treatment of standardized

Skin Substitute	Approved Indication(s)
	split-thickness skin grafts (STSG) donor sites. The authors concluded that Helicoll, as a donor site dressing, is successful in providing pain-free mobility with a measurable healing rate. Study limitations include a small study population and only one wound type (STSG donor site) was evaluated.
Keramatrix	Keramatrix (Molecular Biologicals, LLC) is an open-cell wound dressing used for chronic wounds and ulcers. It is comprised of freeze dried acellular, animal-derived keratin protein. Loan et al. (2016) conducted a controlled study that included 40 patients with superficial or partial thickness burn injuries treated with Keramatrix, compared to 40 historical controls who received standard of care treatment. The results indicated a significantly faster mean healing time in the Keramatrix group than in the control group (8.7 days vs. 14.4 days). Davidson et al. (2013) conducted a randomized controlled trial using a standard care alginate (Algisite) dressing side by side with an experimental dressing (Keramatrix) on 26 patients with partial-thickness donor site wounds. The authors concluded that Keramatrix dressing significantly increases the rate of epithelialization of acute, traumatic partial-thickness wounds in older patients.
Not Medically Necessary	
Affinity	Affinity (Organogenesis Inc.) is a fluid membrane allograft that is intended for clinical use in wound repair and healing. Intended to be applied as an on-lay graft for acute and chronic wounds, including, but not limited to, neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds.
AmnioBand or Guardian	Amnioband and Guardian are human tissue allografts made of donated placental membrane. Although marketed under two different brand names, the products are identical. Intended for interior or exterior wounds including use as a covering for the surgical site. Usage includes various wounds and ulcers and other soft tissue defects. Paggiaro et al. (2018) performed a systematic review to analyze the scientific evidence found in the literature on the use of the amniotic membrane to stimulate DFU healing. DiDomenico et al. (2017) also conducted a retrospective crossover study to evaluate the effectiveness of dehydrated human amnion/chorion allograft (dHACA) to standard of care (SOC). All authors indicated that further studies and comparative clinical trials were needed to establish the effectiveness and safety of Amnioband.

Skin Substitute	Approved Indication(s)
AlloSkin	Alloskin is a specialty allograft derived from epidermal and dermal cadaveric tissue and designed for wound care (Snyder, et al., 2012). Alloskin is a 1:1 meshed, biological cadaveric dermis, which is decellularized and further processed to provide an acellular tissue allograft. These products have been used in acute and chronic wound therapy.
AlloSkin AC	AlloSkin AC is a meshed dermis-only human skin graft that has been decellularized while preserving the natural biologic components and structure of the dermal matrix. The graft provides a favorable microenvironment for bio-ingrowth to begin revascularization and cellular repopulation.
AlloSkin RT	AlloSkin RT meshed human dermal graft is a sterile skin graft with broad clinical applications for acute and chronic wound therapy.
Allowrap	Allowrap is a human amniotic membrane designed to provide a biologic barrier following surgical repair. There are few published studies addressing the use of Allowrap. Therefore, it is not possible to conclude whether Allowrap has a beneficial effect on health outcomes.
AmnioMatrix or BioDMatrix	AmnioMatrix and BioDMatrix are viable human multipotential placental cryopreserved allografts composed of morselized amniotic membrane and amniotic fluid components recovered from the same human donor (CMS, 2013). There are few published studies addressing the use of Amniomatrix or Biodmatrix. Therefore, it is not possible to conclude whether Amniomatrix or Biodmatrix has a beneficial effect on health outcomes.
AmnioExCel or BioDExCel	AmnioExCel (or BioDExCel) is a sterile, resorbable, noncrosslinked dehydrated human amnion membrane allograft composed of an epithelial layer and a stromal layer specifically processed for repair or replacement of lost or damaged dermal tissue (CMS, 2013). Authors from a prospective, open-label, randomized parallel group clinical trial evaluated dehydrated amniotic membrane allograft (DAMA) and SOC compared to SOC alone for the closure of chronic DFUs. The authors concluded the findings suggested DAMA is safe and effective in the management of DFUs but additional research is needed.
ArthroFLEX®	An acellular dermal matrix intended for supplemental support and covering for soft-tissue repair. Carpenter et al. (2017) conducted a study of a small case series to report the clinical results of interpositional arthroplasty using acellular dermal matrix in 4 patients (age 32 to 42 years) for the treatment of advanced ankle osteoarthritis. The primary findings included relief of pain, with improvement in tibiotalar joint range of

Skin Substitute	Approved Indication(s)
	motion from a mean of 16.5° preoperatively to a mean of 31° postoperatively. All 4 patients underwent open arthrotomy of the anterior and posterior tibiotalar capsule with plafond exostectomy and debridement of all deleterious tissue within the ankle capsule, and ArthroFlex acellular dermal matrix applied. The follow-up period ranged from 12 to 18 months. The mean pre- and 12-month postoperative Association of Orthopaedic Foot and Ankle Society hindfoot-ankle scale scores were 35 and 88.5, respectively. The authors concluded that these outcomes suggest that interpositional tibiotalar arthroplasty using an acellular dermal matrix is successful in improving function and range of motion and decreasing pain. This study is limited by a small number of participants and lack of a control arm. Larger randomized controlled trials are needed and should include longer follow-up periods, histologic testing, and arthroscopic evaluations to further assess the durability of this procedure. An ECRI report for Arthroflex Decellularized Dermal Allograft indicated that there is a very small amount of evidence available, and it is not possible to determine the safety and efficacy of ArthroFLEX for repair of rotator cuff tears (ECRI, 2017).
Architect Extracellular Collagen Matrix	Architect is a sterile, extracellular equine derived collagen matrix (ECM) that is intended to treat partial or full thickness skin wounds. Architect PX is a partially stabilized ECM comprised of equine pericardium that is indicated for the local management of moderately to heavy exuding wounds. Indicated for the local management of moderately to heavy exuding wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Moh's surgery, podiatric wounds, dehisced surgical incisions). There are few published studies addressing the use of Architect extracellular matrix for wound treatment. Therefore, it is not possible to conclude whether Architect extracellular matrix has a beneficial effect on health outcomes.
Bio-ConneKt Wound Matrix	Bio-ConneKt Wound Matrix (MLM Biologics) is a bioengineered skin substitute derived from equine Type I collagen. Bio-ConneKt is intended for management of moderately to heavily exuding wounds, including partial and full thickness wounds, draining & tunneling wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, and surgical wounds.

Skin Substitute	Approved Indication(s)
	There are few published studies addressing the use of Bio-ConnecKt for wound treatment. Therefore, it is not possible to conclude whether Bio-ConnecKt has a beneficial effect on health outcomes.
BioDfence and BioDfence DryFlex	BioDfence and BioDfence DryFlex are membrane allografts derived from the human placental tissues for use as a tissue barrier that covers and protects the underlying tissues. The FDA failed to identify any adverse events associated with BioDfence products. Hayes (2018) concluded that there is insufficient evidence to inform decisions in the safety and efficacy of the BioDfence allograft.
AmnioPro; BioSkin; BioSkin Flow; WoundEx Flow;	The **BioFix** Allograft Membrane and Allograft Membrane-Plus are dehydrated, decellularized amniotic membranes, intended for homologous use as a wound covering. **WoundEx Flow** consists of placental connective tissue matrix intended to replace or supplement damaged or inadequate connective tissue. **AmnioPro** Membrane is a human amniotic tissue allograft consisting of dehydrated and decellularized human amniotic membrane. **FlowerPatch** is dehydrated amniotic membrane allograft processed from human amniotic tissues. There insufficient published evidence addressing the use of all dehydrated amniotic membrane human amniotic membranes indicated above. Therefore, it is not possible to conclude whether they have a beneficial effect on health outcomes.
DermACELL	Indications for use include: arterial ulcers, chronic wounds, deep wounds, diabetic foot ulcers, and pressure ulcers.
Dermavest	Dermavest and Plurivest (AediCell) are human amnion/chorion, umbilical cord and placental disk tissue matrixes intended to replace or supplement damaged or inadequate skin tissue and re-stabilize a debrided wound. An advanced wound therapy for burns, chronic diabetic, decubitus (pressure) and venous stasis wounds. There are few published studies addressing the use of Dermavest or Plurivest. Therefore, it is not possible to conclude whether Dermavest or Plurivest has a beneficial effect on health outcomes.
hmatrix PR ADM	Hmatrix PR ADM (Bacterin International, Inc.) is an acellular dermal matrix allograft derived from donated human skin. It is indicated to provide appropriate support and reinforcement for hernia and abdominal wall repairs. There are few published studies addressing the use of hmatrix. Therefore, it is not possible to conclude whether hmatrix has a beneficial effect on health outcomes.
Excellagen	Excellagen is a pharmaceutically formulated fibrillary Type I bovine collagen gel for wound care management.

Skin Substitute	Approved Indication(s)
	Indicated for the management of wounds including partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/ undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears) and draining wounds. There are few published studies addressing the use of Excellagen for wound treatment. Therefore, it is not possible to conclude whether Excellagen has a beneficial effect on health outcomes.
E-Z Derm®	E-Z Derm Biosynthetic Wound Dressing is a porcine-derived xenograft that has been chemically cross-linked with an aldehyde to provide durability and storage. The dermal elements from the original pig dermis are likely all deactivated in the chemical process, unlike the frozen pig dermis which is still available. The studies are limited addressing the use of E-Z Derm for wound care management.
Mediskin®	Mediskin (Brennen Medical, Inc., St. Paul, MN) is a frozen porcine xenograft with a dermal and epidermal layer. The xenograft is 510(k) approved by the FDA as a collagen wound dressing. Per the manufacturer proposed uses include: temporary coverage prior to autograft, partial thickness skin loss, protect meshed autografts, outpatient skin loss, donor sites, skin ulcerations and abrasions. MoInlycke Health Care LLC is the supplier of Mediskin. There are few published studies addressing the use of Mediskin for wound treatment. The use of porcine-derived decellularized fetal skin products (e.g., Mediskin®) has not been established since there are currently no published studies addressing the use of Mediskin.
MemoDerm® Acellular Dermal Matrix; DermaSpan; TranZgraft; IntéguPly	A skin substitute that derives from human allograft tissue and is manufactured using a proprietary gamma irradiation sterilization process. It is markets for use for joint surgeries and chronic diabetic foot ulcers.
PriMatrix® Dermal Repair Scaffold	PriMatrix (Integra Life Sciences, Inc.) is a bovine derived acellular dermal matrix indicated for the treatment of a variety of wounds. There is insufficient scientific evidence regarding the effectiveness of PriMatrix acellular dermal tissue matrix for wound healing. Available evidence is comprised primarily of small, retrospective studies. A systematic evidence review of wound healing products prepared for the Agency for Healthcare Research and Quality found no studies of PriMatrix of sufficient quality to meet criteria for inclusion in the systematic evidence review (Snyder et al, 2012). In a prospective multi-center study, Kavros et al (2014) evaluated the healing outcomes of chronic diabetic foot ulcers treated with

Skin Substitute	Approved Indication(s)
	PriMatrix, a fetal bovine acellular dermal matrix. The authors concluded that the findings of this of this multi-center prospective study suggested that PriMatrix used in conjunction with a center's standard of care wound therapy offers a cost-effective strategy to heal diabetic foot ulcers over that of other advanced wound therapy products based on 12-week healing outcomes as well as number of applications needed to achieve successful closure. The main drawback of this study was the lack of a direct comparison within the study to standard of care as well as to other advanced therapies. The authors stated that the findings from this study should be expanded to include these clinical efficacy comparisons as well as cost-effectiveness comparisons in order to maximize health benefits per dollar spent for the treatment of diabetic foot ulcers.
GammaGraft	GammaGraft (Promethean LifeSciences, Inc., Pittsburgh, PA) is an irradiated human skin allograft acquired from cadaveric donors. Indications for use include: venous stasis ulcers, diabetic foot ulcers, full thickness ulcers, Moh's surgery sites, skin graft donor sites, partial thickness wounds, and areas of dermabrasion. Sivak et al. (2016) conducted a retrospective review of patients undergoing scalp reconstruction utilizing GammaGraft and subsequent skin grafting with GammaGraft. This study is limited by a small number of patients. Further research with randomized controlled trials is needed to validate these findings. The PA DHS Technology Assessment Group (TAG) made an option #4 coverage decision which indicates a lack of peer-reviewed published literature.
Grafix Core and Grafix Prime	Grafix Core and Grafix Prime are extracellular matrix containing growth factors for acute and chronic wounds, including diabetic foot ulcers and burns. For the management of diabetic foot ulcers, venous stasis ulcers and pressure ulcers that have not responded to standard of care therapy. Grafix Core is an allograft containing endogenous mesenchymal stem cells indicated for the treatment of deep chronic wounds, limb salvage procedures, tendon repair and burns. Grafix Prime is an allograft containing endogenous mesenchymal stem cells indicated for upper epithelial layer chronic wounds and burns. Fryberg et al (2017) reported the results of a prospective, multicenter, open-label, and single-arm clinical trial to establish clinical outcomes when Grafix Prime viable cryopreserved human placental membrane (vCHPM) is applied weekly to complex diabetic foot ulcers (DFUs) with exposed deep structures. For patients completing the protocol, the primary endpoint, 100% wound granulation by week 16, was met by 96·3% of patients in a mean of 6·8 weeks. Complete wound closure occurred in 59·3% (mean 9·1 weeks). The 4-week percent area reduction was 54·3%.

Skin Substitute	Approved Indication(s)
	There were no product-related adverse events. Four patients (13%) withdrew, two (6·5%) for non-compliance and two (6·5%) for surgical intervention.
Graftjacket Xpress Flowable Soft Tissue Scaffold	Graftjacket Xpress Flowable Soft-Tissue Scaffold is a micronized (finely ground) decellularized soft tissue scaffold indicated for the repair or replacement of damaged or inadequate integumental tissue, specifically deep, dermal wounds that exhibit tunneling, and extension from the wound base that may extend deep into the tendon and bone. Graftjacket Xpress is a soft tissue graft (reconstituted as a "gel"), which is comprised solely of human dermal tissue, including its native protein and collagen structure and essential biochemical composition. The re-hydrated skin substitute scaffold is placed into the tunnels or tracts, and is intended to produce the same or superior clinical outcomes with a minimally invasive procedure. There is a lack of peer-reviewed published medical literature on the effectiveness and safety of the Graftjacket Xpress. For repair or replacement of damaged or inadequate integumental tissue, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous uses of human integument.
Hyalomatrix PA	Hyalomatrix is a bilayered wound dressing composed of a nonwoven pad made of a benzyl ester of hyaluronic acid, a long-acting derivative of hyaluronic acid, and a semipermeable silicone membrane providing a microenvironment (Snyder, et al., 2012). Hyalomatrix KC Wound Dressing was cleared for marketing under the 510(k) process in July 2001 for "the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. Alvarez and colleagues (2017) provided an analysis of a prospective, parallel, and randomized, single-center study involving 16 subjects in an outpatient wound care center setting. The aim of the study was to evaluate the safety and effectiveness of a hyaluronic acid extracellular matrix for the treatment of chronic VLUs. The authors concluded that the findings of this interim analysis indicated that continuation of the present study is needed. They stated that a more reliable power calculation from these findings forecasts that the inclusion of 50 to 60 participant would be needed to achieve the statistical goal ($p < 0.05$) related to the primary end-point. Indicated for the management of wounds including: partial and full-thickness wounds, second-degree burns, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undetermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh's

Skin Substitute	Approved Indication(s)
	surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, skin tears), and draining wounds.
Integuply	Integuply is an acellular human dermis derived from aseptically processed human allograft skin tissue. It is indicated for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument. Typically used in conjunction with a chronic wound care management regimen for the treatment of diabetic ulcers, Charcot foot ulcers, venous ulcers, trauma wounds, pressure ulcers, partial and full thickness wounds, and surgical wounds.
Marigen Omega3 Acellular Dermal Matrix	Marigen is an omega 3, acellular, dermal extracellular matrix xenograft made from fish (piscine) dermis (CMS, 2014). Indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), and draining wounds.
MatriStem Wound Matrix and MatriStem MicroMatrix	MatriStem (ACell Inc.) products consist of collagens, carbohydrates, and proteins derived from the urinary bladder tissue of pigs. MatriStem is intended for surgical wound care, pelvic floor support or reconstruction, burns, and wound healing. Intended for the management of topical wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. Frykberg et al (2016) reported on an interim analysis of a prospective, multicenter clinical study is to assess the application of MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM) (porcine urinary bladder derived extracellular matrix) compared with Dermagraft (DG) (human fibroblast-derived dermal substitute) for the management of non-healing diabetic foot ulcers (DFUs). A Hayes report for MatriStem Urinary Bladder Matrix Products concluded that the evidence from small studies suggest a potential benefit in wound management, but longer follow-ups and larger studies are needed to confirm these benefits (Hayes, 2017).
Neox 100 Wound Matrix, Neox 1k	Neox Wound Allografts (Amniox® Medical, Inc.) are comprised of two products, Neox CORD 1K Wound Allograft which is a cryopreserved human umbilical cord and amniotic membrane; and

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Wound Matrix and Neox Flo	NEOX 100 Wound Allograft which is a cryopreserved human amniotic membrane indicated for minor and superficial dermal wounds. Neox Flo is a particulate form of Neox. Used in the treatment of partial- and full-thickness wounds including: diabetic foot ulcers, venous leg ulcers, arterial ulcers, and pressure ulcers. There are few published studies addressing the use of Neox Flo and therefore, there is no evidence to conclude beneficial health outcomes. A Hayes report for Neox Wound Allograft concluded that there are very few published studies regarding Neox Wound Allograft and it is not possible to determine the efficacy of this product for the treatment of wounds (Hayes, 2017).
NuShield	NuShield (NuTech) is a protective patch derived from amniotic membrane and is indicated as an adhesion barrier, wound covering, and acts as an adjunct to soft tissue healing, and is intended for use in spinal surgery and as a protective barrier for tendons and nerves following tendon repair. Intended to be applied as an on-lay graft for acute and chronic wounds, including, but not limited to, neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds. There are few published studies addressing the use of Nushield. Therefore, it is not possible to conclude whether Nushield has a beneficial effect on health outcomes.
PuraPly; (formerly called Fortaderm Wound Dressing) PuraPly Antimicrobial Wound Dressing (formerly called Fortaderm Antimicrobial Wound Dressing)	PuraPly is a dressing made of porcine intestinal collagen matrix that is coated with polyhexamethylene biguanide hydrochloride (PHMB) antimicrobial agent. It is intended for wound care management. Indicated for the management of: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Moh's surgery, post-laser surgery, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears) and draining wounds. There are few published studies addressing the use of PuraPly or PuraPly Antimicrobial for wound treatment. Therefore, it is not possible to conclude whether PuraPly or PuraPly Antimicrobial has a beneficial effect on health outcomes. According to Hayes (2018), There is insufficient evidence to determine the safety and efficacy of PuraPly for wound care.
Repriza	Repriza is a prehydrated, ready-to-use, acellular dermal matrix derived from human allograft tissue. Repriza is a surgical implant and does not have any other use outside of the surgical setting. There is no indications that are specific to VLUs or DFUs. Also, there are few published studies addressing the use of Repriza. Therefore, it

Skin Substitute	Approved Indication(s)
	is not possible to conclude whether Repriza has a beneficial effect on health outcomes.
Revitalon	Revitalon is a human tissue allograft made of donated amniotic membrane derived from the inner lining of donated placenta. Revitalon can be used as a covering for full-thickness wounds, damaged membranes, and as a dressing for burns. It is comprised of native human amnion and chorion consisting of collagen types I, III, IV, V, VI, laminin, fibronectin, nidogen, and proteoglycans. Indicated for the management of wounds including: diabetic ulcers and venous ulcers. There are few published studies addressing the use of Revitalon for wound treatment. Therefore, it is not possible to conclude whether Revitalon has a beneficial effect on health outcomes.
Talymed	Talymed is a wound care management product composed of shortened fibers of poly‐N‐acetyl glucosamine (pGlcNAc) isolated from microalgae. It is indicated for the management of a range of serious, complex wounds. Kelechi et al. (2012) conducted a randomized controlled investigator blinded pilot study to evaluate the efficacy, safety, and tolerability of Talymed among patients with venous leg ulcers (VLUs) compared to treatment with standard care plus pGlcNAc or to standard care alone. It was concluded that the results of this pilot study suggest that the pGlcNAc advanced wound-healing technology is well tolerated and effective. This study was limited by the small sample size and patients unblinded to treatment allocation. Further research with randomized controlled trials is needed to validate these findings. Indicated for the management of wounds including: diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds (e.g., donor sites/grafts, post-Moh's surgery, post-laser surgery), abrasions, lacerations, traumatic wounds healing by secondary intention, chronic vascular ulcers, and dehisced surgical wounds.
TenSIX Acellular Dermal Matrix	TenSIX is an acellular dermal matrix with natural histomorphology preserved. TenSIX is derived from aseptically processed cadaveric human skin tissue that is terminally sterilized. Hayes (2018) indicated that human acellular matrix allografts have are primarily used for breast reconstruction surgeries. There are few published studies addressing the use of TenSIX. Therefore, it is not possible to conclude whether TENSIX has a beneficial effect on health outcomes. Chronic diabetic foot ulcers

Skin Substitute	Approved Indication(s)
TranZgraft Acellular Dermal Matrix (Memoderm)	TranZgraft (AZIYO® Biologics) is an acellular collagen matrix intended for repair of sports related injuries, including tendons and ligaments. There are few published studies addressing the use of TranZgraft. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes. Intended use is for ulcer repair.
Unite Biomatrix	Unite Biomatrix is a non-reconstituted collagen dressing used to maintain the wound bed in the healing phase thereby allowing for health granulation tissue and wound closure. Unite Biomatrix may be applied to discrete areas of the wound that have not yet healed satisfactorily. Unite Biomatrix is packaged in a solution and is available pre-fenestrated or non-fenestrated. Unite Biomatrix differs from other skin products in that it is composed of decellularized equine pericardial implants. The use of equine-derived decellularized collagen products has not been established as shown by the lack of evidence on the subject. Intended for the management of moderately to severely exudating wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears), and surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Moh's surgery, podiatric wounds, dehisced surgical incisions).
XCM Biologic Tissue Matrix	XCM Biologic Tissue Matrix is a sterile non-crosslinked 3-D derived from porcine dermis. It is indicated for the use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists. A systematic review and meta-analysis was conducted to evaluate the clinical and patient-centered outcomes of XCM Biologic tissue matrix compared with other mucogingival procedures (Atieh, 2016). The authors reported limited evidence that may improve aesthetic satisfaction, reduce postoperative morbidity and shorten operating time. Further long-term randomized controlled trials are required to endorse the supposed advantages of XCM.

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Policy History

Date	Activity
10/17/2016	Initial policy developed
03/14/2017	QI/UM Committee approval
05/01/2017	Provider effective date
08/09/2017	Added Disclaimer Statement in opening of medical policy. EHS Revisions: Added Issue Date to opening policy box; Added 'Covered' and 'Noncovered' to procedure code table in Attachment B; Added 'Covered' to diagnosis code table in Attachment C; added 'Informational' to Table in Attachment D.
12/13/2017	Clinical Review; Added ABI to Definition section; updated criteria under Procedure, added The diabetic foot ulcer is free of infection; AND Wound must have adequate circulation and presence of acceptable peripheral pulses or as evidenced by ankle-brachial index (ABI) of 0.65 or greater in the limb being treated. An index of greater than 0.45 is needed to heal; Added MariGen as a non-covered product; Added reference
03/13/2018	QI/UM Committee Review Approval
04/25/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables under CODING REQUIREMENTS
05/15/2018	Provider effective date
03/12/2019	Annual Review: Reformatted the criteria under procedures for skin substitutes that are covered for A. and B. to include the covered skin substitute products; included updated literature to the summary of literature; added medically necessary and not medically necessary skin substitutes and coverage explanation to the summary of literature; Removed the C codes due to nonuse Added HCPCS code Q4153 to noncovered procedure code section; removed HCPCS codes from the covered procedure codes section and moved the HCPCS codes to the noncovered procedure codes section based on the updated literature findings (Q4110, Q4112, Q4115, Q4117, Q4119, Q4122, Q4123, Q4125, Q4126, Q4127, , Q4134, Q4135, Q4136, Q4137, Q4138, Q4139, Q4140, Q4141, Q4142, Q4143, Q4146, Q4147, Q4148, Q4149, Q4150, Q4151, Q4155, Q4156, Q4157, Q4159, Q4160, Q4161, Q4162, Q4163,); Added HCPCS code to the noncovered procedure code section; Removed HCPCS code Q4119 from procedure codes due to AMA deletion; Removed HCPCS code Q4120 due to burn only indication, not wound care; Removed HCPCS code Q4130 AND Q4172 due to breast only indication, not wound care; Removed all breast neoplasm ICD-10 diagnoses codes; Added rationale and literature to Attachment C to for each skin substitute; removed the hyperlinks from all references.
03/12/2019	QI/UM Committee Review Approval
05/06/2019	Provider Effective Date
03/21/2019	Code updated: Q4119, Q4129, and Q4172 were deleted CMS HCPCS codes and were removed from policy.