

Clinical Policy: EpiFix Wound Treatment

Reference Number: CP.MP.140

Last Review Date: 03/19

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Description

EpiFix[®] (MiMedx Group) is a bioactive tissue matrix allograft composed of dehydrated human amniotic/chorionic membrane that is used as an allograft material (or tissue graft) to treat nonhealing wounds. It is prepared using a proprietary process by which placental tissues are gently separated, cleaned of viable cells, reassembled, and dehydrated, preserving factors important in healing. EpiFix is processed from human tissue according to the American Association of Tissue Banks (AATB) standards, and is regulated as a human cell, tissue, or cellular or tissue-based product.

Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation[®] that EpiFix is **medically necessary** for the treatment of chronic foot ulcers when all of following criteria are met:
 - A. Age \geq 18 years;
 - B. Type I or type II diabetes;
 - C. Foot ulcer surface area* $> 1\text{cm}^2$ and $< 25\text{cm}^2$;
 - D. Ulcer duration of ≥ 4 weeks, unresponsive to standard wound care;
 - E. No clinical signs of infection;
 - F. Ulcer does not probe to tendon, muscle, capsule or bone;
 - G. Serum creatinine < 3.0 mg/dl;
 - H. HbA1c $< 12\%$;
 - I. Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test (TcPO₂) $\geq 30\text{mmHg}$, or ankle-brachial index (ABI) between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg.
**Surface area can be calculated by multiplying width in cm by length in cm.*
- II. It is the policy of health plans affiliated with Centene Corporation that continued treatment with EpiFix is **not medically necessary** when the ulcer fails to heal by $\geq 50\%$ within the first 6 weeks of treatment. Treatment beyond 12 weeks is considered **not medically necessary** regardless of wound status.
- III. It is the policy of health plans affiliated with Centene Corporation that treatment with EpiFix for any other types of nonhealing wounds is considered **investigational**.

Background

Lower extremity ulceration is a common complication for patients with diabetes. Diabetic foot ulcers lead to some form of amputation in 20% of patients and are associated with higher morbidity and mortality. The presence of peripheral vascular disease, neuropathy and poor blood glucose control contribute to the development of lower extremity wounds, their slow rate of healing and their propensity to recur. Evidence-based guidelines for the management of lower extremity diabetic ulcers include moist dressings, debridement, wound offloading, infection

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control and implementation of advanced wound therapies if the ulcer does not decrease in size by 40% or more after 4 weeks of standard therapy.¹

EpiFix is proposed to promote cellular migration to enhance soft tissue repair in acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness wounds; venous, diabetic, pressure, and chronic vascular ulcers; trauma wounds, including burns; and surgical wounds. EpiFix is not indicated for wounds that probe to bone or are infected. EpiFix is typically ordered and applied by wound care specialists in an outpatient setting.

The general steps involved in using EpiFix include:

- Surgical debridement of infected or decaying tissue until the wound base is visible and has good blood flow.
- If necessary, trimming of the EpiFix membrane to produce a 1-millimeter (mm) overlap with the wound margin. The product may be applied either dry or moistened with saline.
- Confirmation of the correct orientation of the EpiFix membrane, which is then placed over the wound and secured with adhesive strips.
- Application of a nonadherent contact layer followed by a moist dressing.

The membrane typically incorporates into the wound bed within 2 weeks of application.

The overall quality of evidence evaluating EpiFix is low, however, among diabetic patients with chronic foot ulcers, studies although limited, reported a greater reduction in mean wound size and higher proportion of wound healing among patients treated with EpiFix compared with those treated with standard care.² A systematic review of randomized clinical trials (RCTs) of skin grafts or tissue replacements for treating foot ulcers in people with diabetes, concluded the incidence of completed closure of diabetic foot ulcers was significantly improved for the skin grafts or substitutes compared with standard care. No specific type of skin graft or tissue replacement showed a superior effect on ulcer healing over another type of skin graft or tissue replacement.³

A prospective, randomized, controlled, parallel group, multi-center clinical trial of 60 patients reported that dehydrated human amnion/chorion membrane (i.e., EpiFix) is superior to standard wound care (SWC) and bioengineered skin substitutes (i.e., Apligraf) in achieving complete wound closure within 4–6 weeks.⁴ Rates and time to closure at a longer time interval and factors influencing outcomes remained unassessed; therefore, the study was continued in order to achieve at least 100 patients. With the larger cohort, the authors compared clinical outcomes at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers treated with weekly applications of Apligraf (n = 33), EpiFix (n = 32) or standard wound care (SWC) (n = 35) with collagen-alginate dressing as controls. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SWC, respectively (adjusted P = 0.00019). Subjects treated with EpiFix had a very significant higher probability of their wounds healing compared to SWC alone. Mean time-to-heal within 12 weeks was 47.9 days with Apligraf, 23.6 days with EpiFix group and 57.4 days with the SWC alone group.¹

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The evidence to assess the effectiveness and safety of EpiFix for the treatment of other types of nonhealing wounds, including venous leg ulcers is very limited. A multicenter, randomized, controlled study of 84 patients evaluating the safety and efficacy of one or two applications of dehydrated human amnion/chorion membrane allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers reported at 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure. After 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls. Venous leg ulcers treated with allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone.⁵

A more recent multicenter randomized, controlled trial of 109 participants with non-healing full-thickness VLUs, compared EpiFix as an adjunct to multilayer compression therapy to multilayer compression therapy alone reported similar results. Within 12 weeks of randomisation, 31 of 52 (60%) VLU patients receiving EpiFix completely healed compared with a healing rate of 20 of 57 (35%) in those treated with standard care alone. At the 16 -week follow-up visit, complete VLU healing was observed in 37 of 52 (71%) and 25 of 57 (44%) of those treated with EpiFix or standard care, respectively.¹¹

A Hayes comparative effectiveness review on skin substitutes for chronic venous leg ulcers concluded the overall quality of the evidence assessing the efficacy of skin substitutes incremental to standard wound management alone is low. Evidence suggests that more patients with chronic venous leg ulcers that do not heal with standard care alone experience complete healing when a bilayer human skin equivalent or allograft is used in addition to standard care. Benefits with other skin substitutes have not been clearly demonstrated in RCTs. Evidence does not suggest any 1 skin substitute performs better than any other, due to null findings or lack of replication of positive findings in more than 1 study because the studies rarely made the same comparison.¹⁵

Clinical Guidelines from the Society for Vascular Surgery and the American Venous Forum on the management of venous leg ulcers note that numerous tissue constructs are available for use in chronic wounds that employ either human tissue (amniotic membrane, cryopreserved skin) or animal tissue (bladder, fetal bovine skin, others) in an effort to accelerate VLU closure. Currently, they suggest the use of a porcine small intestinal submucosa tissue construct in addition to compression therapy for the treatment of venous leg ulcers that have failed to show signs of healing after standard therapy for 4 to 6 weeks.¹²

Coding Implications

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CPT codes considered medically necessary per policy criteria when billed with Q4186

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CPT® Codes	Description
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)

HCPCS codes considered medically necessary per policy criteria

HCPCS Codes	Description
Q4186	EpiFix , per sq cm

ICD-10-CM diagnosis codes that support medical necessity

ICD-10-CM Code	Description
E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E10.621	Type 1 diabetes mellitus with foot ulcer
E11.621	Type 2 diabetes mellitus with foot ulcer
E13.621	Other specified diabetes mellitus with foot ulcer

CPT codes NOT medically necessary when billed with Q4186

CPT® Codes	Description
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)

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed. Specialist reviewed	04/17	04/17
Added recommendation from the Society for Vascular Surgery and the American Venous Forum to background section of the policy.	03/18	03/18
Revised I.I TcPO2 ≥ 30mmHg. Replaced deleted code Q4131 with new code Q4186. References reviewed and updated. Specialist review.	03/19	03/19

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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