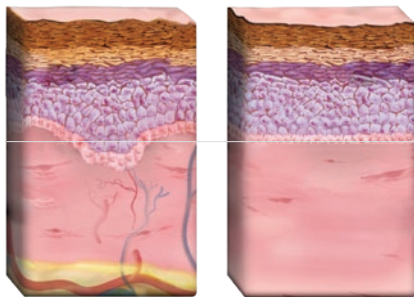


Rediscover healing that remains ahead of its time.

Bioengineered with living cells to transform wounds from chronic to acute, Apligraf® is backed by unmatched clinical evidence in healing venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs).¹⁻⁸

Description

- ▶ Apligraf is bioengineered with living cells that are bioactive and poised to heal.^{9,10}
- ▶ Apligraf looks, functions, and responds like healthy human skin.^{2,9,11,12}



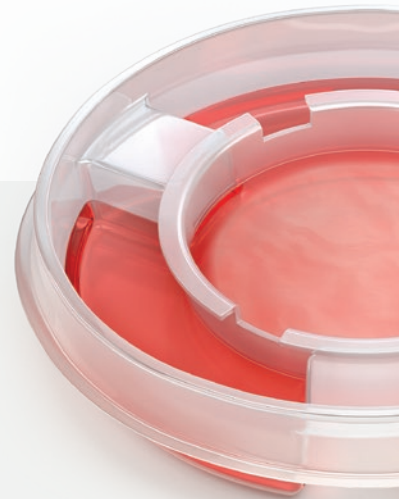
Normal skin

Apligraf

Epidermal layer: Contains living keratinocytes and stem cells* that provide potent healing signals (growth factors/cytokines).^{2,11,12}

Dermal layer: Contains living fibroblasts that proliferate and produce human collagen and other ECM proteins as well as growth factors/cytokines.^{2,11,12}

* Keratinocyte stem cells are key contributors to the signaling profile of Apligraf.

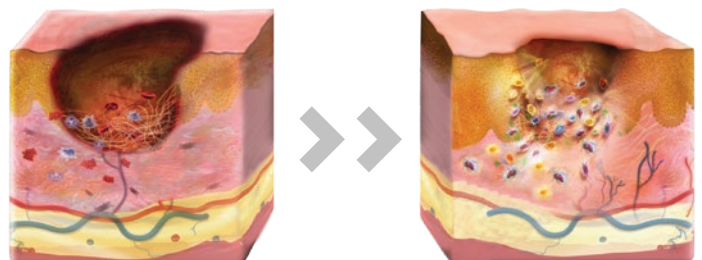


Indications

- ▶ Apligraf is the **ONLY** product FDA-approved to heal VLUs and DFUs.²
 - For VLUs, Apligraf may be used after 4 weeks of failed conventional therapy²
 - For DFUs, Apligraf may be used after 3 weeks of failed conventional therapy²

Evidence of mechanism of action

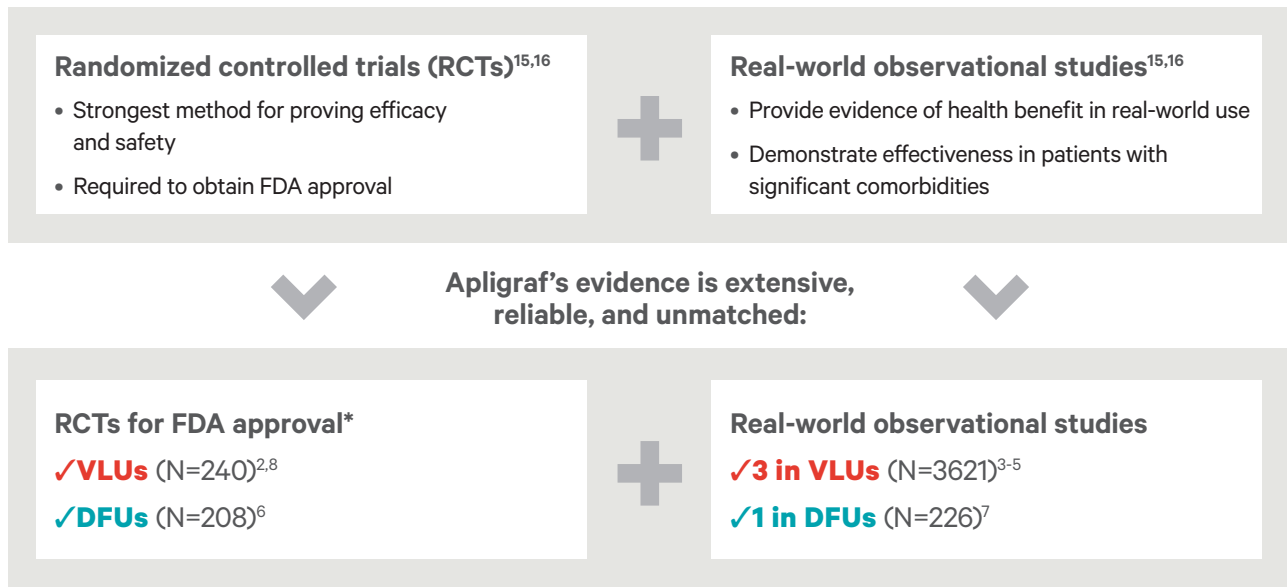
- ▶ The living cells of Apligraf stimulate a potent healing mechanism, help restore normal healing functions, and put the wound back on track to heal.^{1,9,10,13}
- ▶ In an RCT in VLUs, Apligraf transformed the wounds (N=24) from chronic to acute; specifically Apligraf:
 - Activated keratinocytes at the wound edge¹
 - Restored fibroblast function at the wound base, thus normalizing ECM production and MMP balance¹⁴
 - Corrected and regulated growth factor signaling^{1,9,13}
 - Downregulated fibrosis formation¹⁴



Clinical Evidence

▶ Apligraf® is backed by unmatched clinical evidence in healing VLU and DFUs faster.²⁻⁸

Reliable data equals:



*Only Apligraf has conducted RCTs resulting in FDA approval for VLUs and DFUs.^{2,6,8}

Ns for RCTs=number of patients; Ns for real-world observational studies=number of wounds

Insurance coverage

▶ Apligraf has unsurpassed access for patients.[†]

100%

of Medicare contractors cover Apligraf treatment for VLUs and DFUs⁸

100%

of commercial medical policies cover Apligraf treatment for VLUs and DFUs⁸



The coverage information provided shall not be construed as a statement, promise, or guarantee that reimbursement will be received. Reimbursement requirements are subject to change at any time. Check with your local payer regularly.

[†] Insurance coverage varies by payer and is subject to change at any time. Confirm with your current applicable payer policies for up-to-date Apligraf coverage requirements and policies.

Please refer to the Apligraf Package Insert for complete prescribing information and contraindications.

References: 1. Stone RC, et al. *Sci Transl Med*. 2017;9(371). doi:10.1126/scitranslmed.aaf8611. 2. Apligraf [package insert]. Canton, MA: Organogenesis Inc; 2017. 3. Marston WA, et al. *Wound Repair Regen*. 2014;22(3):334-340. 4. Treadwell T, et al. *Adv Wound Care*. 2018;7(3):69-76. 5. Sabolinski ML, et al. *J Comp Eff Res*. 2018;7(8):797-805. 6. Veves A, et al. *Diabetes Care*. 2001;24(2):290-295. 7. Kirsner RS, et al. *Wound Repair Regen*. 2015;23(5):737-744. 8. Data on file. Organogenesis Inc. 9. Milstone LM, et al. *Wounds*. 2000;12(5 suppl A):12A-19A. 10. Falanga V, et al. *J Invest Dermatol*. 2002;119(3):653-660. 11. Schmid P. *Wounds*. 2000;12(5 suppl A):4A-11A. 12. Carlson M, et al. *Tissue Eng Part A*. 2011;17(3-4):487-493. 13. Brem H, et al. *Surg Technol Int*. 2003;11:23-31. 14. Stone RC, et al. *Wound Repair Regen*. 2019. doi:10.1111/wrr.12778. 15. Carter MJ, et al. *Adv Skin Wound Care*. 2009;22(7):316-324. 16. Horn SD. *JAMA*. 2006;296(22):2731-2732.

Apligraf Essential Prescribing Information.

Visit www.apligraf.com for complete prescribing information and contraindications.

Numbers in parentheses () refer to sections in the main part of the product labeling. **Device Description:**

Apligraf is supplied as a living, bi-layered skin substitute manufactured from cells processed under aseptic conditions using neonatal foreskin-derived keratinocytes and fibroblasts with bovine Type I collagen.

(1) **Intended Use/Indications:** Apligraf is indicated for use with standard therapeutic compression in the treatment of uninfected partial and/or full-thickness skin loss ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. (2) Apligraf is indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness foot ulcers of neuropathic etiology of at least three weeks duration, which have not adequately responded to conventional ulcer therapy and extend through the dermis but without tendon, muscle, capsule or bone exposure.

(2) **Contraindications:** Apligraf is contraindicated for use on clinically infected wounds or in patients with known allergies to bovine collagen or with known hypersensitivity to the components of the Apligraf agarose shipping medium. (3, 4, 5, 8) **Warnings and Precautions:** If the expiration date or product pH (6.8-7.7) is not within the acceptable range DO NOT OPEN AND DO NOT USE the product. A clinical determination of wound infection should be made based on all of the signs and symptoms of infection. (4, 5) **Adverse Events:** All reported adverse events, which occurred at an incidence of greater than 1% in the clinical studies are listed in Table 1, Table 2 and Table 3. These tables list adverse events both attributed and not attributed to treatment.

(6) **Maintaining Device Effectiveness:** Apligraf has been processed under aseptic conditions and should be handled observing sterile technique. It should be kept in its tray on the medium in the sealed bag under controlled temperature 68°F-73°F (20°C-23°C) until ready for use. Apligraf should be placed on the wound bed within 15 minutes of opening the package. Handling before application to the wound site should be minimal. If there is any question that Apligraf may be contaminated or compromised, it should not be used. Apligraf should not be used beyond the listed expiration date. (9) **Use in Specific Populations:** The safety and effectiveness of Apligraf have not been established in pregnant women, acute wounds, burns and ulcers caused by pressure. **Patient Counseling Information: VLU** patients should be counseled regarding the importance of complying with compression therapy or other treatment, which may be prescribed in conjunction with Apligraf. **DFU** patients should be counseled that Apligraf is used in combination with good ulcer care including a non-weight bearing regimen and optimal metabolic control and nutrition. Once an ulcer has healed, ulcer prevention practices should be implemented including regular visits to appropriate medical providers.

Treatment of Diabetes: Apligraf does not address the underlying pathophysiology of neuropathic diabetic foot ulcers. Management of the patient's diabetes should be according to standard medical practice. **How Supplied:**

Apligraf is supplied sealed in a heavy gauge polyethylene bag with a 10% CO₂/air atmosphere and agarose nutrient medium. Each Apligraf is supplied ready for use and intended for application on a single patient.

To maintain cell viability, Apligraf should be kept in the sealed bag at 68°F-73°F (20°C-23°C) until use. Apligraf is supplied as a circular disk approximately 75 mm in diameter and 0.75 mm thick. (8) **Patent Number:** 5,536,656

Manufactured and distributed by: Organogenesis Inc. Canton, MA 02021 REV: December 2017 300-111-10