DermGEN™

Clinical Treatment Protocol for Diabetic Foot Ulcers

DeCell Technologies
ADVANCED REGENERATION

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1 Product Description and Use

DermGEN™ is a tissue-based product derived from donated human skin. Human skin is processed using DeCell's proprietary decellularization process (prECM™) that removes donor cellular materials—the main causes of immune rejection, disease transmission and inflammatory reaction—while leaving growth factors and the structural extracellular matrix (ECM) intact. Further, DeCell's patented prECM™ process also sterilizes the tissue enhancing safety and healing.

DermGEN™ is intended for use in the promotion of healing and tissue regeneration in dermal wounds such as diabetic ulcers (DFU's). The unique characteristics of the extracellular matrix scaffold provided by DermGEN™ acts to support and promote host cell recruitment, new blood vessel formation and new tissue formation at the wound site resulting in complete healing.

2 Patient Qualifications for DFU Treatment with DermGEN™

2.1 Qualification criteria:

A patient **will be considered eligible** for treatment with DermGEN™ **if each of the following criteria** is satisfied:

- Type I or II diabetes ($HbA1_C$ between 5.0 to 12 mmol/L)
- Ulcer is categorized as Wagner Grade 1 or 2
- Ulcer shows no sign of tissue infection (i.e., cellulitis or osteomyelitis)
- Adequate perfusion to the extremity determined **by at least one** of the following:
  - ✓ Palpable pedal pulses
  - ✓ Transcutaneous oxygen measurement at the dorsum of the foot ≥30 mm Hg
  - ✓ Ankle-brachial index ranging from ≥ 0.5
  - ✓ At least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries
- Patient and social support (e.g., family, caregiver) ready and willing to participate and comply with follow-up regime
- Patient willing to be involved in self-care (e.g., keep dressing dry at home) required during treatment
- Patient willing to use appropriate off-loading device during treatment

2.2 Disqualification criteria:

A subject **will not be considered eligible** for DermGEN™ treatment **if any one of the following criteria** is self-reported or identified in their medical record:

- Obvious clinical signs and symptoms of ongoing tissue infection (i.e., cellulitis) or bone infection (i.e., osteomyelitis)
- Ulcer is over Charcot deformity
- Ulcer is not classified as diabetes-related
- Affected foot shows evidence of gangrene
- Ulcer has tunnels or sinus tracts that cannot be completely debrided
- Presence of malignant disease not in remission for 5 years or more
- The individual is undergoing chemotherapy/radiation therapy
- The individual received radiation therapy within 30 days of planned treatment
- The individual is taking an immunosuppressant medication (e.g., corticosteroids, immunosuppression or cytotoxic agents), or is anticipated to require such agents during treatment
- Presence of acute or chronic hepatitis, liver disease, anemia, serum albumin <2.0 gm/dL, or has alkaline phosphatase or LDH at twice the normal upper limit
- The individual has a history of a bleeding disorder or is taking blood thinner medication

2.3 Timing for Use of DermGEN™

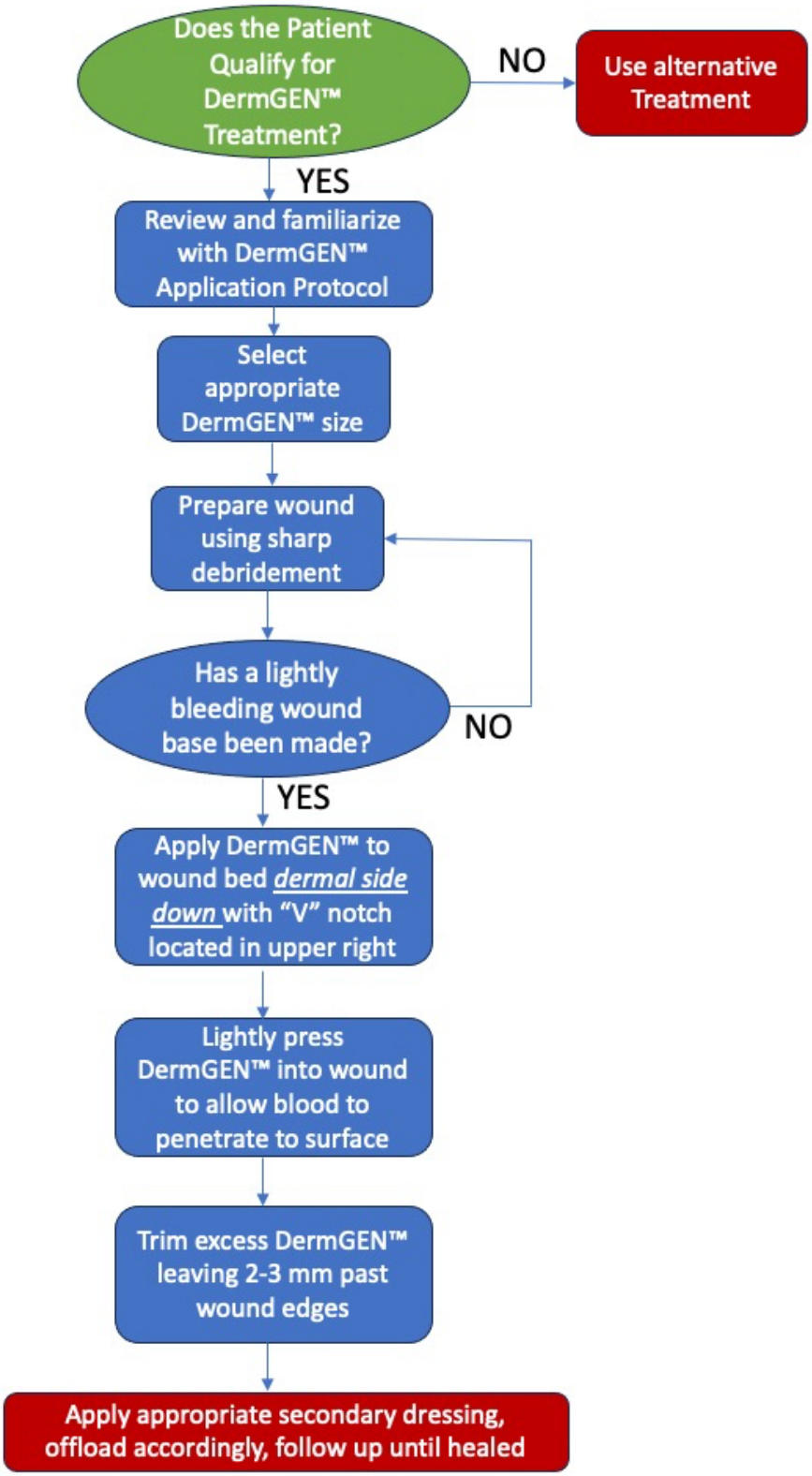
DermGEN™ can be applied to DFU wounds on qualified patients at any time with earlier treatment after initial presentation of the wound providing the best opportunity to ensure healing. Alternative advanced treatments, such as DermGEN™, are recommended to be used if a 40-50% reduction in wound size is not achieved after 4 weeks of standard wound care.[1,2]

If you have any questions about a patient's eligibility for treatment with DermGEN™, please contact DeCell Technologies Inc. at (902) 223-2179, pfgratzer@decelltechnologies.com to speak to a Clinical Advisor.

Below is a Application Flowchart to provide an overview of the main steps required for proper DermGEN™ use in treating DFU's. Detailed instructions on wound bed preparation, DermGEN™ sizing, application, secondary dressings to be used with DermGEN™ and follow-up procedures are given in the Sections 3 and 4. By carefully following these detailed instructions, you ensure that your patient can achieve complete wound healing in the least amount of time.

[1] *Chronic Wound Care Guidelines*, The Wound Healing Society
[2] *The Management of the diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in Collaboration with the American Medical Association and Society for Vascular Medicine,* Hingorami, A. et al., J Vasc Surg 2016;63:3S-21S., Recommendations 5 and 9.

DermGEN™ Application Flowchart



3 DermGEN™ Application Instructions

DermGEN™ is provided in a hydrated state and does not require rehydration.

**** DermGEN™ is provided with a ***basement membrane surface that repels blood*** and ***a dermal surface that absorbs blood***. To identify the surfaces, a small "V" notch is provided that indicates the basement membrane on the upper surface when the "V" notch is located in the upper right corner of the graft. When applied to the wound bed in a grafting procedure, ***the dermal side should be placed against the wound bed,*** with the basement membrane side facing up.

DermGEN™ is secured in a sterile inner pouch. **Only the inside of the inner pouch is to be considered sterile**. A foil outer pouch and final outer packaging is used for shipping to protect the package from damage. Normally, only ***one*** application of DermGEN™ is required for complete healing.

1. It is imperative that the Diabetic Foot Ulcer (DFU) wound site be properly prepared to ensure the best possible result with DermGEN™. Proper sharp or surgical debridement is recommended to remove all dry and necrotic tissue on the wound. The debrided wound should have edges made up of living tissue and have a good bleeding base. (Figure 1)

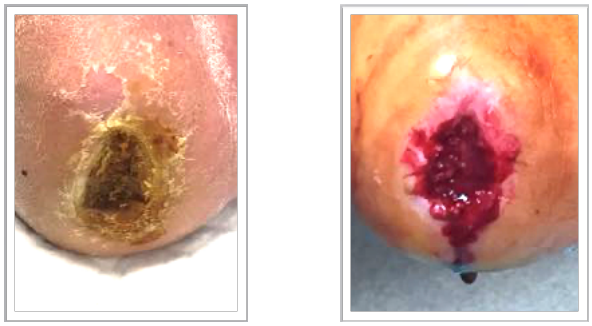


Figure 1. DFU before *(left)* and after *(right)* proper debridement

2. Peel back the outer package (Non-sterile) and remove DermGEN™ from the inner pouch using sterile gloves/forceps and place directly onto the wound. DermGEN™ needs to be applied to the wound site with the ***dermal side*** (blood absorbing side) in contact with the bleeding wound (**see note above). (Figure 2)

Once the pouch containing DermGEN™ has been opened and exposed, the tissue shall be transplanted within 30 minutes, otherwise, it should be discarded.

*****Each piece of DermGEN™ can be used on only one patient.*****

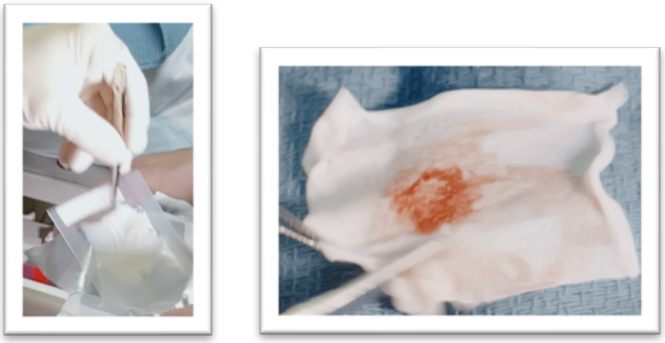


Figure 2. Removal of DermGEN™ from package *(left)* and showing dermal side identified by absorbed blood patch *(right)*

3. DermGEN™ may be aseptically trimmed to fit the dimensions of the application site. The tissue can be shaped with scissors or scalpel allowing for an approximate 3-5 mm border beyond the wound edges. (Figure 3) With the dermal side in contact with the bleeding wound bed, you should

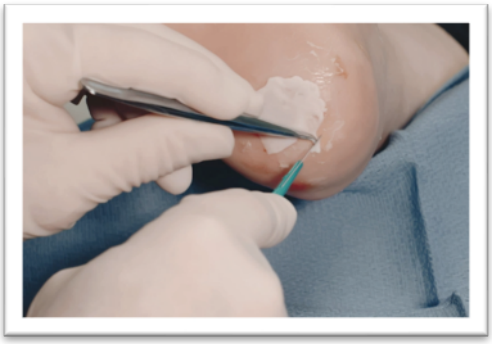


Figure 3. Trimming of DermGEN™ to wound size.

notice that DermGEN™ is "sucked" down into the wound and blood will appear at the exposed top surface through natural pores in the product. DermGEN™ can be lightly pressed into the wound until blood on the surface is seen as blood absorption and good wound bed contact are needed for proper healing to occur (Figure 4). If DermGEN™ does not adhere securely to the wound, the wrong surface (basement membrane side) of the product may be in contact with the wound and should be corrected to the ***dermal side***.

4. DermGEN™ normally ***does not require*** securing with sutures or staples to the surgical site if utilized properly. In some applications, minimal securing of DermGEN™ to the surgical site may be required due to the location of the area treated (e.g. distal end of toe). Place the properly trimmed DermGEN™ with the dermal side in contact with the bleeding wound bed.

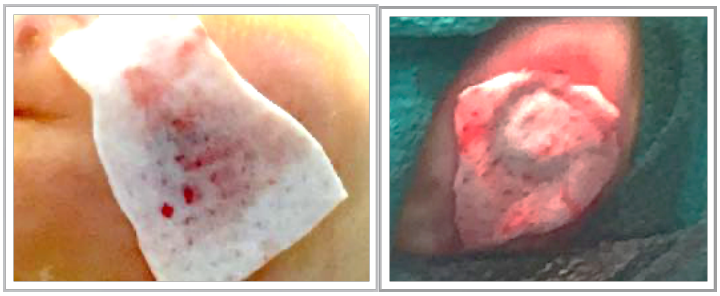


Figure 4. DermGEN™ in good contact with the wound bed showing blood at its the top surface.

5. The wound can now be dressed with wound dressing materials that possess a non-adherent contact layer and a moisture controlling foam layer(s)—see Section 4 below for examples. It is recommended that dry gauze then be wrapped around the secondary dressing to add slight pressure to the wound site in order to prevent movement of DermGEN™ during the first 1-2 weeks of healing. For deeper wounds, a bolster can be added to help hold DermGEN™ in place for the 1-2 weeks.. Once DermGEN™ is applied to the wound, it does not need to be re-applied—***one*** application is normally required for complete healing to occur.
6. ***Off-loading of the wound site is critical to the healing performance of DermGEN™***. It is recommended that a contact cast or removable off loading boot be used until the wound has healed. In all cases, best practices on off-loading techniques should be consulted and followed that are most appropriate to the location of the wound and with patient compliance in mind.
7. Follow-ups with patient should occur at weekly (at minimum) to check wound healing progress and make secondary dressing changes. For circumstances where moisture or exudate is predicted or seen to be higher (e.g. using a total contact cast in summer months), more frequent secondary dressing changes—such as every 3-4 days—is recommended ***to avoid maceration and product failure.***

4 Secondary Dressing Materials and Follow-Up

At minimum, weekly changes of ***only the secondary wound dressing materials*** (e.g. Mepilex® and gauze) are required until healed. Once the old secondary dressing is removed, ***Do Not wash or debride the DermGEN™ treated area***. Simply apply a new secondary dressing.

DermGEN™ works best if the wound is not touched after application.

For circumstances where moisture or exudate is predicted or seen to be higher (e.g. using a total contact cast in summer months), more frequent secondary dressing changes—such as every 3-4 days—is recommended ***to avoid maceration and product failure.***

Secondary Dressings used in conjunction with DermGEN™ can be either *a combination of a separate non-adhesive contact layer and a separate moisture controlling foam* (see Figure 5) or a *combination product with both the non-adhesive contact layer and moisture controlling foam all in one product* (see Figure 6).

Non-Adhesive Wound Contact Layer examples:

- Mepitel®, Mölnlycke Health Care
- Adaptic
- Silflex, Advancis Medical
- Comfitel™, DermaRite®
- Dimora Silicone Wound Contact Layer, Dimora

Moisture Controlling Foam examples:

- Tegaderm™ Foam Dressing, 3M™
- Exufiber, Mölnlycke Health Care

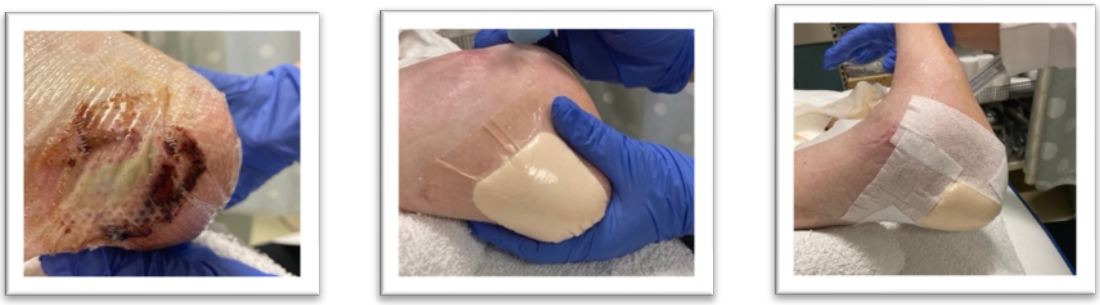


Figure 5. A secondary dressing consisting of a separate non-adherent contact layer (*left)* topped with a moisture controlling foam *(centre)*. Tape is used to help secure the dressings *(right).*

Combination Dressing (non-adhesive contact layer + moisture control foam) examples:

- Allevyn® Classic Non-Adhesive Dressing, Smith and Nephew
- Mepilex® Border, Mölnlycke Health Care
- Tielle Essential™ Silicone Dressings, 3M+KCl
- Aquacel®, Convatec

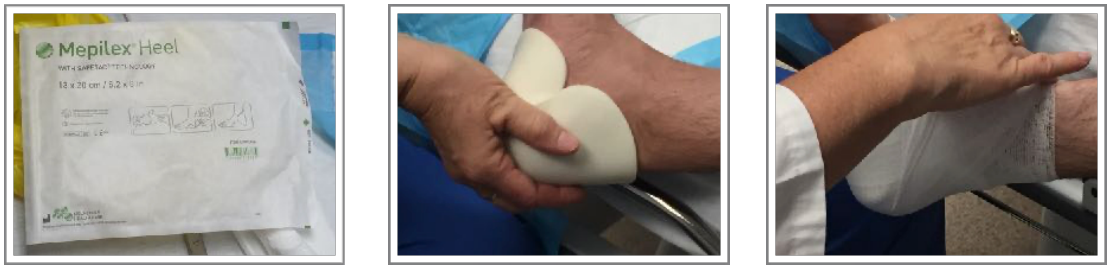


Figure 6. A secondary dressing consisting of an all-in-one product with non-adhesive contact layer and absorbent foam backing (*left)*, Secondary dressing applied to the wound area *(centre)* and a dry gauze wrap to help secure the dressing *(right)*.

5 Healing Progression of DFU's Treated with DermGEN™

Because DermGEN™ operates differently in healing wounds, the typical and expected look of healing wounds will differ from that seen with Standard of Care (SOC) that includes weekly debridement, cleansing and wound dressing changes.

The expected and desired look of good wound healing progress after DermGEN™ application can be confused with undesired healing progression that requires attention. ***DermGEN™ works best if the wound is not touched after application.*** Although the wound may appear to require cleaning or debridement, these procedures are to be avoided. The only intervention that may be required after DermGEN™ application is if an active infection is present.

Below are provided examples of normal and desired appearances of the wound bed after treatment with DermGEN™ and following expected wound healing timelines.

Below are shown examples of early stages of DemGEN™ incorporation and remodelling with blood products from the bleeding wound base during application to the wound bed. The ***incorporation and interaction of blood and blood products is important and desired*** to promote and accelerate healing with DermGEN™. With DermGEN™ use, the wound bed needs to have a blood on the surface that is important to help to reset

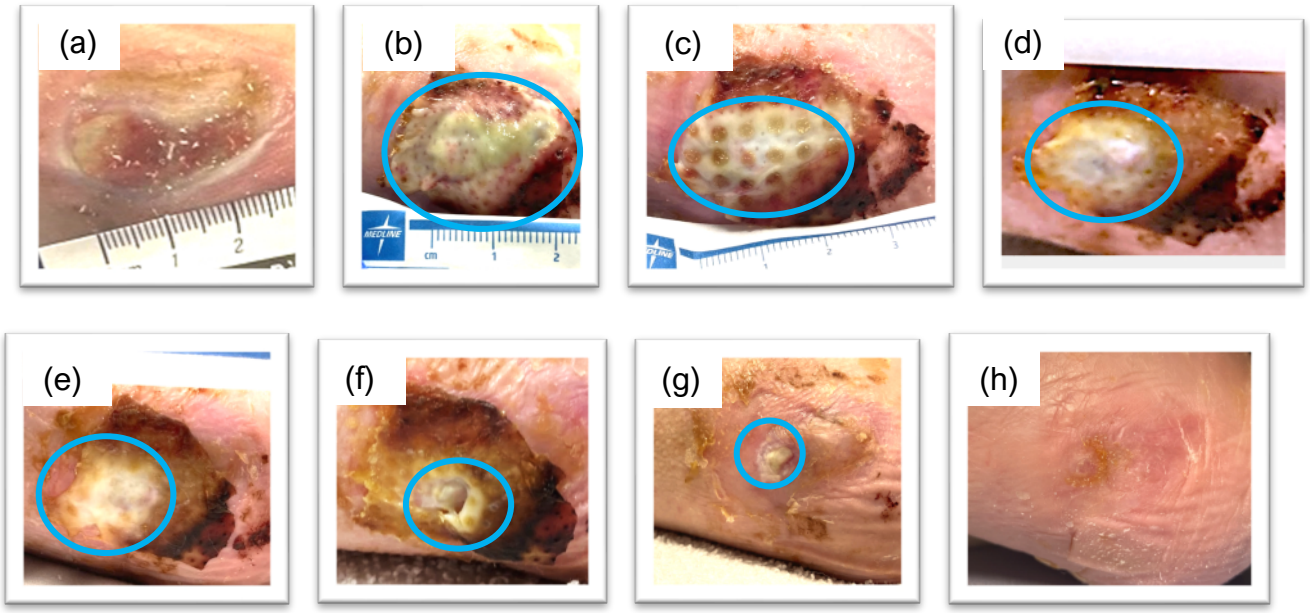


Figure 7. Example of DFU healing progression after DermGEN™ application. (a) wound bed before treatment. (b) 4 days after application. Surface appears moist and off-white to yellow in colour. (c) 1 week after application, edges where re-epithelialization is occurring indicated by the drying and brown portions of the wound. The circled area is still undergoing healing as indicated by moist, off white area *(circled)*. (d) 2 weeks after application. More dry, brown area of re-epithelialization and final healing appear with the moist, off white actively healing area *(circled)* decreasing in size. (e) 3 weeks, (f) 4 weeks, (g) 5 weeks and (h) 7 weeks after application. Eventually, moist and dry areas are replaced by healthy new skin tissue.

the inflammatory cycle moving towards healing and stimulate cells to regenerate new blood vessels and

tissue. The presence of blood in the wound bed and its interaction with DermGEN™ also facilitates its early incorporation and securing it into the wound bed. As you can see, ***wound healing with DermGEN™ is different*** from that seen and managed with Standard of Care. It is these differences in wound appearance with DermGEN™ treatment that are normal and desired while also reflecting the manner in which DermGEN™ enhances, promotes and accelerates wound healing.

For further information on healing with DermGEN™, please go to www.dermgen.ca and the document *"What Healing Looks Like with DermGEN™".*

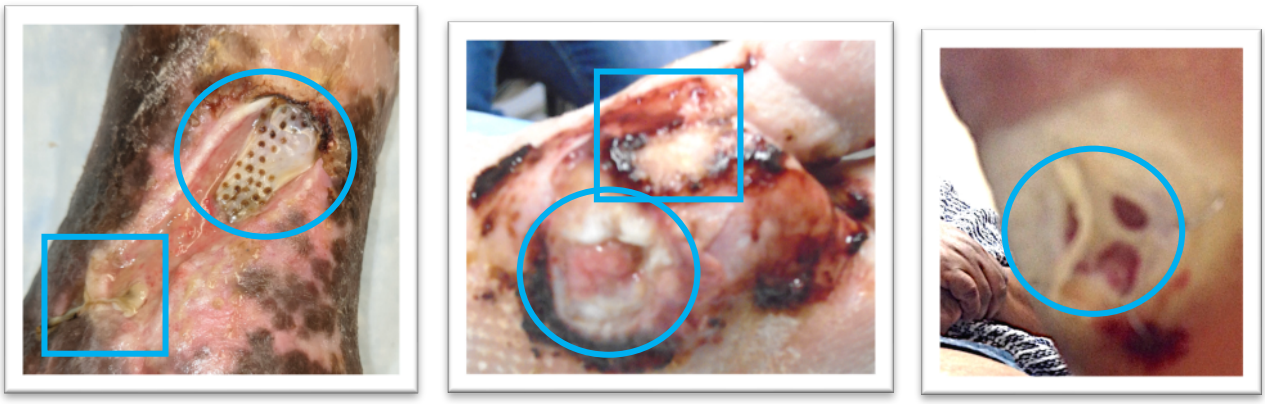
6 Potential Issues During Healing

6.1 Detachment of DermGEN™

Normally, if proper application procedures are utilized with DermGEN™ and the dermal side of the product is in contact with the wound bed, DermGEN™ will be adhered to and incorporated into the wound bed after 1-2 weeks. If DermGEN™ completely detaches from the wound in less than 3 weeks after application, the wound bed can be prepared again by debridement and another DermGEN™ piece applied. If DermGEN™ detaches completely after more than 3 weeks after treatment, the wound may be left without DermGEN™, treated with standard of care and monitored to see if continued healing occurs. There have been cases where the presence of DermGEN™ in the wound—even for limited period of time— has been able to promote healing. If no further healing progress is observed, another piece of DermGEN™ can be applied.

6.2 Too Much Moisture and DermGEN™ Maceration.

Too much moisture in the wound will cause maceration of DermGEN™. Maceration of DermGEN™ is identified by the presence of a significant odour, a very "mushy" like consistency, loss of integrity and partial or complete detachment from the wound bed. See Figure 8 for examples.



(a) (b) (c)

Figure 8. Examples of macerated DermGEN™ graft due to excessive moisture in the wound. (a) Note large detached piece *(circled*), smaller soft and degraded piece *(square)* of DermGEN™ and overall wet appearance of wound bed. (b) Note white appearence of wound edge and exposure of wound bed after detachment of DermGEN *(circled).* The square area shows yellowish and mushy remaining DermGEN™ graft piece. (c) The sounding skin and DermGEN™ graft appear yellow to white in color due to excessive moisture. Note the detachment and loss of integrity of the DermGEN™ graft *(circled)*.

6.3 Too Little Moisture and DermGEN™ Drying Out

Too little moisture in the wound area can cause DermGEN™ to dry out to the point where it will not stay in connection with the underlying wound bed and can lift off and possibly entrap moisture below it. Look to use a less absorbent moisture controlling foam. See Figure 9 for examples.

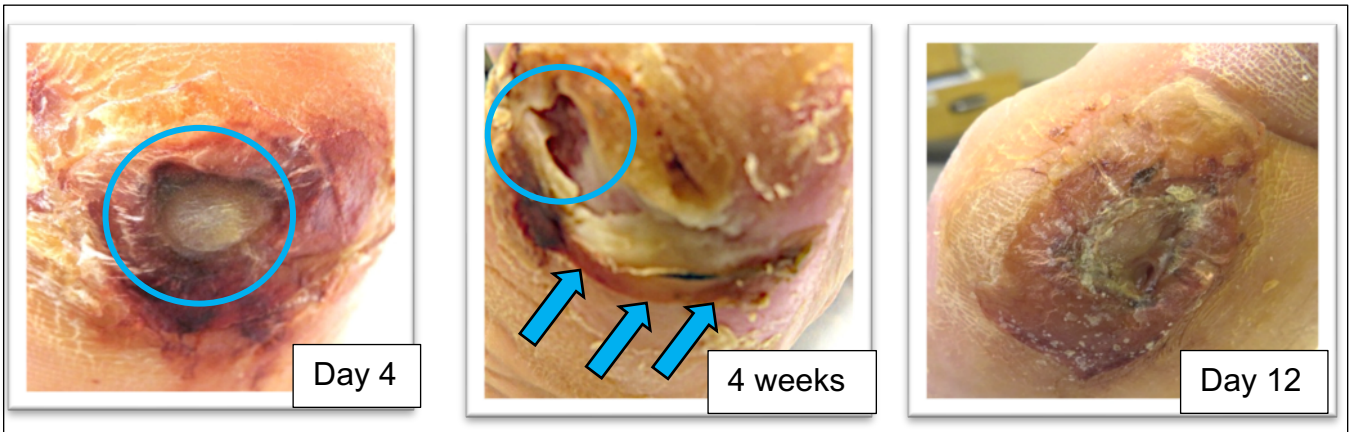


Figure 9. Examples of dried DermGEN™ graft due to lack of moisture in the wound area.
(a) Note extreme dryness around central wound area and dry central area (blue circle)
(b) Note the lifted dry graft edges exposing underlying wound bed (blue circle) and tracking of moisture into peri-wound area (arrows).
(c) Note extreme dryness of the entire wound area.

7 Further Information

For further information on DermGEN™, please visit www.dermgen.ca. Any questions about DermGEN™ and its use can be sent to info@decelltechnologies.com .