Epicel®
(cultured epidermal autografts)

Treatment & Care Guidelines

Mark
Treated with Epicel

RECOVERING WITH EPICEL®

cultured epidermal autografts

www.Epicel.com

HUMANITARIAN DEVICE: Epicel® (cultured epidermal autografts) is authorized for use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. The effectiveness of the device for this use has not been demonstrated.

IMPORTANT SAFETY INFORMATION: Epicel is contraindicated in patients with a history of anaphylaxis following exposure to vancomycin, amikacin, and amphotericin, as trace quantities of these anti-infective agents may remain in the Epicel autograft. Epicel should not be used in patients with known sensitivities to materials of bovine or murine origin. It is contraindicated for use on clinically infected wounds. Because Epicel is manufactured with and contains residual amounts of murine cells, FDA considers it a xenotransplantation product. Therefore, recipients should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans because there is a potential risk of carrying an infection that is transmitted from mouse cells to humans.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

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Indication

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Squamous cell carcinoma (SCC) has been reported in patients with burn injury after being grafted with Epicel. Although SCC is a known complication of burn scars, the role of Epicel in the causation of SCC cannot be excluded.

The Epicel product is intended solely for autologous use. Patients undergoing the surgical procedure associated with Epicel are not routinely tested for transmissible infectious diseases. Discontinue use if the patient shows evidence of allergic reaction.

If clinical signs of infection are present or develop, do not apply Epicel until the infection is adequately treated.

The effectiveness of Epicel has not been proven in clinical studies.

The long-term safety of Epicel is unknown. Over the past 27 years, the mortality from all causes was 13% before hospital discharge.

Men and women who intend to have children should be advised that the effects, if any, of Epicel on fetal development have not been assessed. In addition, the safety of Epicel has not been studied in pregnant and nursing women.

Patient information supplied by attending burn teams from 1989 to 1996 reported the adverse events of highest incidence as: death (13%), infection (13.8%), graft tear (7.8%) or graft blister (4.2%) and drainage (3.3%). Some of these events may have been due to the underlying burn injury and not the device itself.

From June 1998 through September 2015 adverse events received by Genzyme Biosurgery (predecessor in interest to Vericel) and Vericel Corporation were similar to the previously identified adverse events. Events that were reported in ≥ 1% of patients included multi-organ failure (6.6%), sepsis (5.2%) infection (4%) and skin graft failure/graft complication (2.7%). The relationship of these events to Epicel has not been established.

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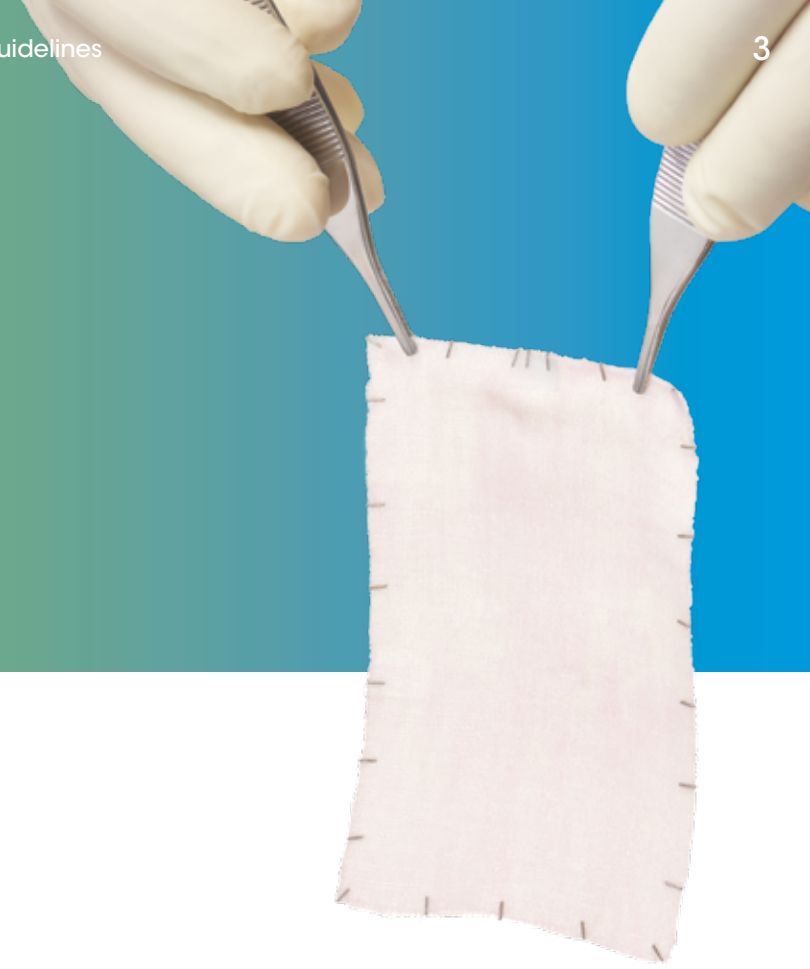
The information provided in this document is intended for educational purposes; it is not a substitute for medical care nor should it be construed as medical advice. The guidelines incorporate recommendations from burn care experts based on their extensive clinical experience with Epicel. Although time frames are suggested, it is more important specific goals are attained before progressing. Decisions should be up to the discretion of the individual health care provider.

Support for your practice

Vericel representatives are thoroughly trained and experienced in all aspects of the procedures leading to grafting success with Epicel. To request additional information, please call **1-800-CEA-SKIN** (1-800-232-7546).



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Planning

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Epicel patient considerations

Epicel is a graft grown from a patient's own skin. Epicel grafts provide skin replacement for adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%. Enough skin to cover the patient's entire body can be grown from two full-thickness postage stamp-sized biopsies of healthy skin.

Epicel can cover a significant area in a single treatment. Consider Epicel to expand your treatment options in large burns 30%+ TBSA.

Epicel is valuable when autograft is limited due to:

- Allocation of autograft for key functional areas[1]
- Overtaxed or unsuitable harvest sites[2]
- Undesirable or limited quality skin
- Concomitant injuries or disease
- A history of skin conditions
- A need to limit donor re-harvesting procedures

Taking a biopsy within the first 24-48 hours after patient admission is needed for Epicel to be available for your patients

- There is never a financial cost for taking or processing an Epicel biopsy.
- A single Epicel order can cover an area up to 5,760 cm^2 in a single treatment with the possibility to treat larger surface areas.
- Epicel can be ordered for subsequent surgeries without the need for additional biopsies

To order a Vericel Skin Biopsy Transport Kit, call **1-800-CEA-SKIN** (1-800-232-7546) or contact your Vericel representative

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Manufacturing process: biopsy to Epicel graft

The patient's own skin cells are cultured ex vivo for approximately 17 days to produce Epicel.

- **Flexible scheduling**—If grafting surgery needs to be delayed, skin cells can be cryopreserved for future use. At a later date, the cells can be thawed, grafts prepared, and shipped with a 14-day advance notice.
- **Flexible ordering**—Epicel can be ordered for subsequent surgeries without the need for additional biopsies.
- **Flexible quantity**—A customized amount of Epicel grafts can be generated and shipped to your facility in a single order. A Vericel representative is available to help determine the appropriate use and number of grafts per patient.

Epicel Manufacturing Process

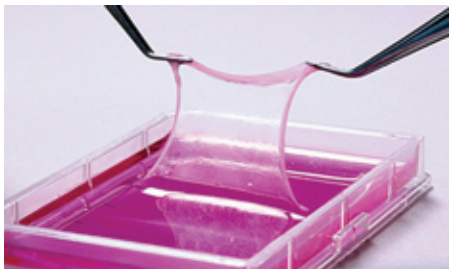
STEP 1
BIOPSY PREPARATION
Subcutaneous skin layers are removed, sample is cut into smaller fragments, and rinsed.

STEP 2
CELL ISOLATION
Skin fragments are placed in an enzyme solution that separates the epidermis from the dermis to isolate the keratinocytes (cells).

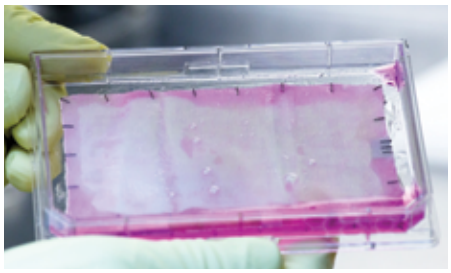
STEP 3
CELL EXPANSION
Keratinocytes are placed in flasks with a growth medium where they double in number every day forming epidermal autografts.

STEP 4
EPICEL GRAFT ASSEMBLY
After sterility testing, the epidermal autografts are placed onto gauze backing and packaged for transport to the operating room.

Increasing cell confluency



Confluent sheet of skin cells just prior to being affixed to a petrolatum gauze backing



Epicel is attached to a rectangular petrolatum gauze backing with titanium surgical clips

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Epicel treatment planning

Epicel can be used in combination with a variety of treatments prior to and during application.[3,4] Consider the appropriate temporary and permanent covering options and timing throughout the duration of a patient's care.

Wound bed preparation*

Dermal Substrate Options

Temporary wound covering

Dermal Substitutes

Dermal substitutes remain in place until full engraftment occurs. Apply per the product manufacturing guidelines.

Cadaver Allograft

Allograft can help achieve temporary wound closure.[5,6,7]

Epicel grafting preparation

Epicel Underlay Options

Substrate and structure for Epicel grafts

Wide mesh autograft

Provides native cell signaling between the patient's dermis and Epicel. Meshing ratios of 4:1, 6:1, and 9:1 have been used with success.**

MEEK micrografting

MEEK micrografting creates autograft "islands" allowing skin to grow from the margins.

Allodermis technique

The allograft dermis, or "allodermis", is retained and serves as a substrate for Epicel.

* Wound bed preparation occurs while Epicel is being manufactured. Temporary coverings typically take approximately 2-3 weeks to fully engraft, aligning with the approximate 17 day ex vivo culturing of the patient's skin cells during Epicel manufacturing. Always apply products per the manufacturing guidelines.

** A 6:1 skin autograft mesher may be available to your burn center for use with Epicel patient cases. Ask your Vericel representative for more information on the Vericel Burn Care autograft mesher placement program.

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Pregrafting

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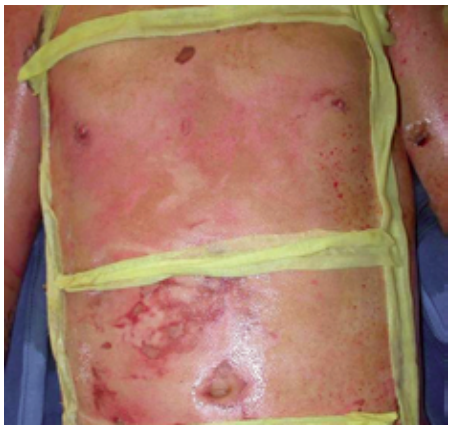
Patient admission & temporary coverage

- Early burn wound excision and closure have been shown to improve survival, reduce the infection rate, and shorten hospital stays.[8,9]
  - Ideally, the patient is taken to the OR within 72 hours of admission.
  - Plan for total excision by postburn day 5-7.
- To reduce fluid loss and bacterial invasion during the period of immunosuppression following a burn injury, an excised wound can be covered with cadaver allograft or dermal substitutes.



A patient with burns covering 60% of the total body surface area prior to debridement

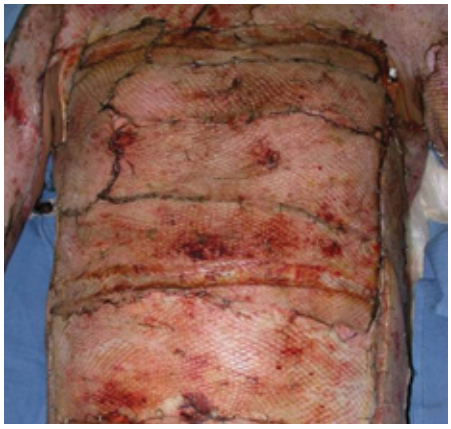
Dermal Substrates are temporary coverings that remain in place until full engraftment occurs—usually 2-3 weeks depending on the dermal substrate utilized.

Dermal Substitutes (including NovoSorb® BTM, PriMatrix®, and Integra®) should always be applied per the product manufacturing guidelines.

Cadaver Allograft allows dermal elements to be incorporated into the wound bed over a period of weeks to create a positive take with Epicel.[5,6,7]

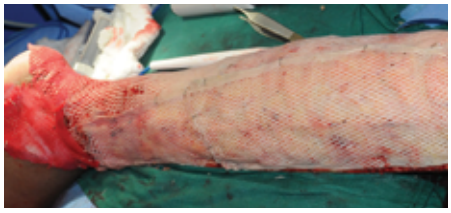
Excised wounds can be covered with 2:1 meshed, but not expanded, allograft, or a dermal substitute.[7,8,10,11]

Full engraftment is critical to provide a highly vascular and clean wound surface necessary for successful placement of Epicel.



A burn patient after debridement, covered with allograft

Autograft donor site	**Available**	**Wide mesh autograft** (4:1, 6:1) or **MEEK micrografting** (9:1) can serve as an underlay for Epicel grafts
	Unavailable	**Engrafted allograft dermis** can serve as an underlay for Epicel grafts[5]



Allograft used as a wound bed covering after debridement

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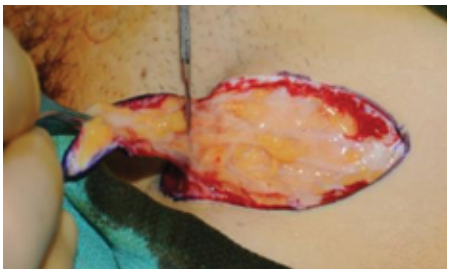
Biopsy procurement

The Epicel biopsy can be taken during the same operation as cleaning the burn or during the initial burn excision procedure.

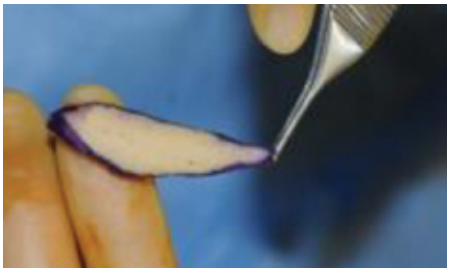
If the initial excision procedure is delayed, the biopsy can be taken at bedside under local anesthesia. Anesthetic should be injected circumferentially, not directly into the biopsy site.



Procuring a full-thickness biopsy

Taking an Epicel biopsy:

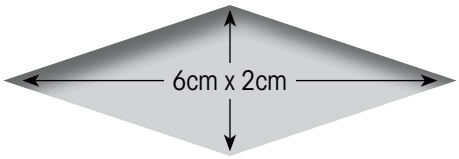
1. The biopsy site should be shaved to remove hair, thoroughly washed, and swabbed with 70% alcohol.
2. Prepare the area with a sterile normal saline rinse. If it is suspected that the biopsy site is highly contaminated, the preparation sequence may be repeated to remove the excessive bacterial bioburden.
3. Procure two full-thickness biopsies measuring approximately 6cm long by 2cm wide from different sites on the burn patient's undamaged, non-diseased skin. Biopsy site suggestions include the axilla and groin, but any non-burned area may serve as a biopsy site.



A biopsy measuring approximately 6cm long by 2cm wide

After a biopsy has been taken:

1. Complete the Biopsy Transmittal Notice for Epicel.
2. Package biopsy according to Vericel Skin Biopsy Transport Kit Instructions for Use.
3. Call Vericel Customer Care at **800-CEA-SKIN** for biopsy pickup. Vericel Customer Care is available 24 hours a day, 365 days a year and will schedule a courier to pick up the Vericel Skin Biopsy Transport Kit. Please do not ship the Vericel Skin Biopsy Transport Kit.



Contents of the Vericel Skin Biopsy Transport Kit

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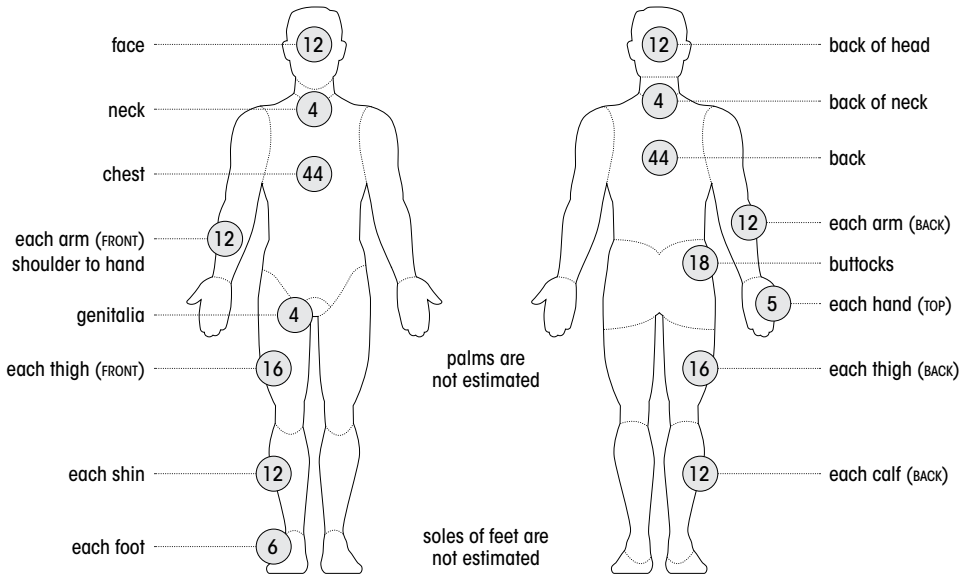
Epicel graft planning

Planning and early identification of Epicel graft treatment areas is critical.

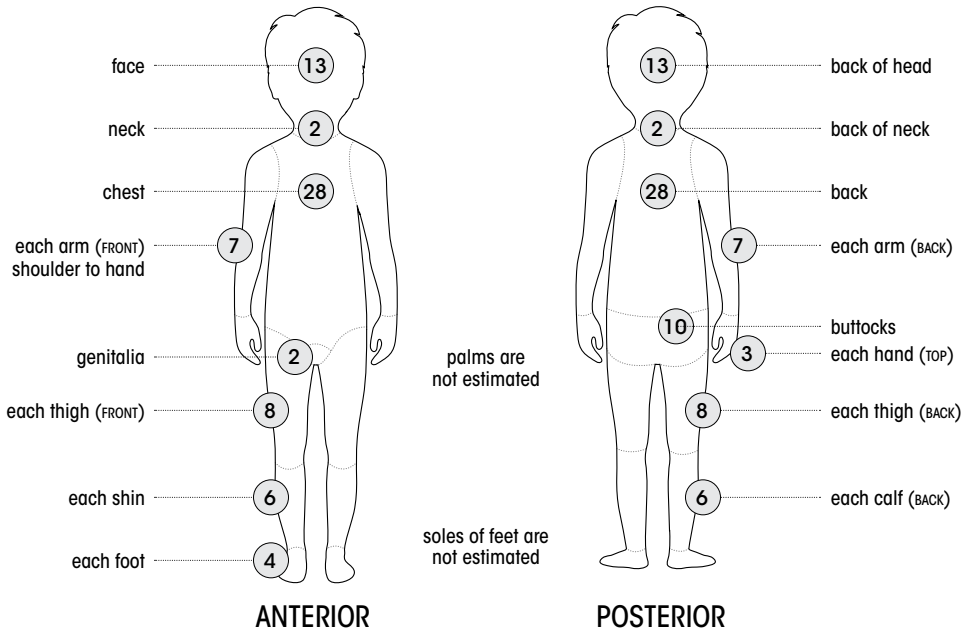
- In order to determine the appropriate number of grafts needed, it is important to consider the treatment plan and to measure those areas intended for Epicel to ensure graft availability at the time of application.
- Be sure to consider burn areas that may declare further or additional outlying treatment areas.
- Vericel representatives are available to discuss your graft treatment plans and support early identification of Epicel treatment areas.

Note: The graft estimates in the diagram are determined by the formula TBSA/60cm², based on the average Epicel graft size of 60cm². Epicel grafts must measure a minimum of 50cm² to leave the manufacturing facility.

Graft estimates for typical adult patient (example: 5'8, 180 lbs., 20,000 cm² TBSA)



Graft estimates for typical pediatric patient (example: 4'2", 90 lbs., 12,000 cm² TBSA)



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Wound bed maintenance

- Ideally, the patient is taken to the OR within 72 hours of admission.
- Excised wounds can be covered with allograft or a dermal substitute until full engraftment.
  - Patients should be taken back to the OR every 3-5 days for repeat debridement and replacement of non-adherent allograft.
  - Dressings containing silver have been successfully used in preoperative wound bed preparation for Epicel, but their use should be discontinued at least 24 hours prior to grafting to reduce silver levels on the wound bed.
  - Please consult your individual burn unit protocols for additional guidance on dressings.
  - For dermal substitutes, please refer to their product manufacturing guidelines for maintenance protocols.
- Epicel is more susceptible to wound bed conditions and bacterial colonization than split-thickness autograft.[12]
  - Routine sensitivity testing of wound cultures (swab or preferably quantitative culture for bacteria and fungi) of the areas to be grafted with Epicel are recommended.
  - *Please see page 12 for a list of recommended anti-infective agents to use with Epicel and a list of anti-infective agents to avoid.*
- Range-of-motion exercises should be performed routinely to maximize the functional range of the patient's joints.

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Anti-infective agents

Anti-infective agents tested on Epicel in vitro with no significant inhibitory effects[12]

AGENT	MAX DOSE*
Amphotericin B	24 µg/mL
Bibiotic (Polymyxin B Sulfate and Bacitracin Zinc)	200 U/mL, 50 U/mL
Cefoperazone	100 µg/mL
Ciprofloxacin	5 µg/mL
Gentamicin Sulfate	1 mg/mL
Neomycin Sulfate	2 mg/mL
Nystatin	480 U/mL
Polymyxin B Sulfate	1000 U/mL
Polysporin® (Polymyxin B Sulfate and Bacitracin Zinc)	200 U/mL, 10 U/mL
Triple Antibiotic (Polymyxin B Sulfate, Bacitracin Zinc and Neomycin Sulfate)	100 U/mL, 25 U/mL, 0.6 mg/mL
Tobramycin Sulfate	6 µg/mL
Vancomycin Hydrochloride	1 mg/mL

*Maximum dose that did not inhibit keratinocyte growth and differentiation resulting in the number of growing colonies greater than or equal to 50% of the control and the average growing colony size greater than or equal to 50% of the control.

In addition, there is a limited degree of clinical experience with topical administration of the following agents: bacitracin zinc, fluconazole, imipenem, ketoconazole, and mupirocin.

Anti-infective agents tested on Epicel in vitro with significant inhibitory effects should be avoided[12]

AGENT
AK-Spore HC (Polymyxin B sulfate, Neomycin sulfate, Hydrocortisone)
Acetic Acid
Clotrimazole
Miconazole

Anti-Infective agents that have known inhibitory effects on EPICEL should be discontinued at least 48 hours prior to Epicel grafting.

Contact your Vericel representative for more information on appropriate use of topical antibiotic and antifungal agents with Epicel

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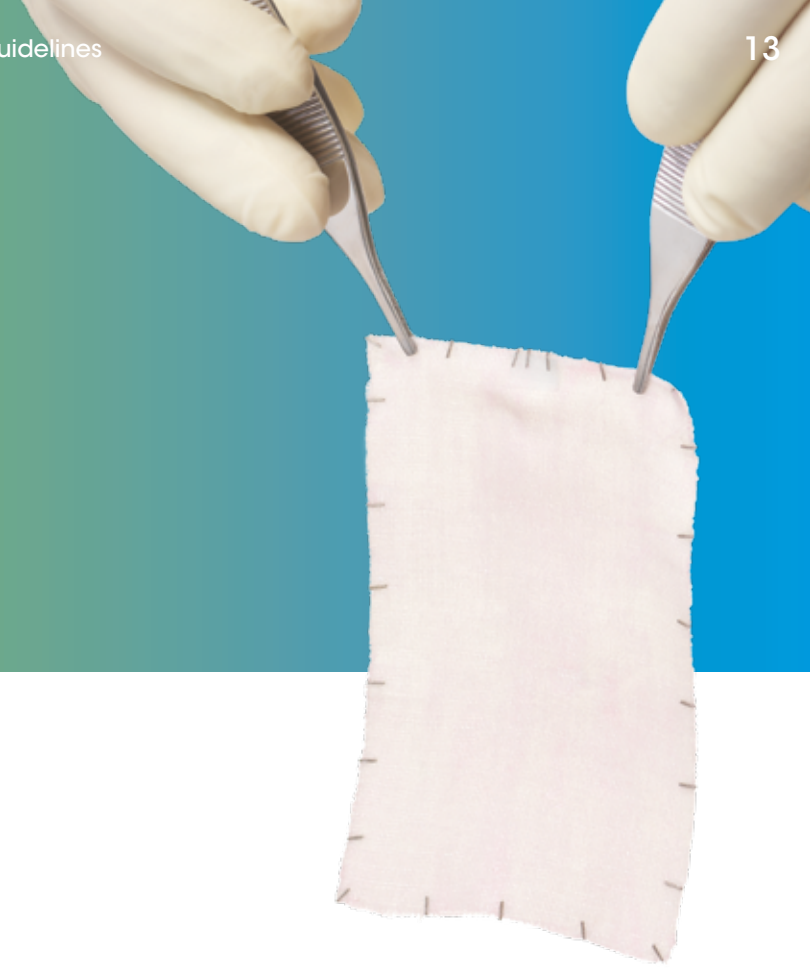

Grafting

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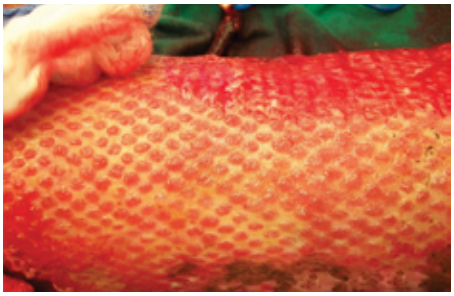
Surgical preparation of wound bed for Epicel

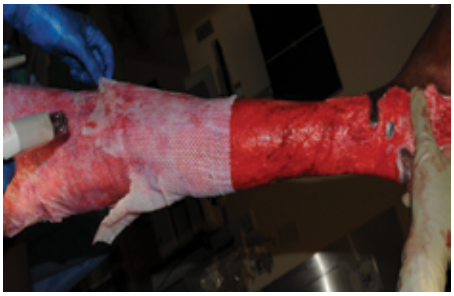
- 24-48 hours prior to the Epicel grafting date the patient should be taken to the OR for final wound bed preparation.
  - Any devitalized or granulation tissue should be removed to achieve a clean, well-vascularized wound bed.
  - Epicel engraftment is dependent on a clean (low/no bacterial count) vascularized wound bed with complete homeostasis.
  - A clinical infection will impede graft take.
- Prior to Epicel grafting, the prepared wound bed should be covered and kept moist with sterile saline dressings or protected with a non-adherent dressing. Cadaver skin has been shown to reduce drying and desiccation of the underlying tissue.
  - If using a dermal substitute, prepare according to the manufacturer's prescribed directions for use.
- Chlorhexidine gluconate (CHG) is cytotoxic to Epicel and should not be used on Epicel patients.
  - CHG use should be discontinued at least 48 hours prior to Epicel grafting.
  - Current alternative options for skin preparation include Betadine®, Vashe®, or Puracyn®. Alternative options for autograft harvest lubrication include mineral oil, PrimaDerm®, or sterile lubricating jelly.

Final wound bed prep 24-48 hours prior to Epicel grafting can:

- Decrease surgery time and blood loss on Epicel grafting day.
- Provide final wound bed assessment and wound cultures.
- Allow PT/OT to do final measurements and assessments before Epicel placement



Fully engrafted allograft with a petechial bleeding pattern arising from the dermis after removal of the alloepidermis



A clean, vascularized wound bed is protected with moist dressings

NO CYTOTOXIC AGENTS

Do not use any product containing chlorhexidine gluconate (CHG)

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Epicel grafting preparation

- To ensure maximum cell viability, it is important to schedule the Epicel grafting procedure as a first case or as early in the day as possible.
- Epicel grafts are delivered the morning of surgery, accompanied by the Vericel representative. To ensure maximum cell viability a 24-hour expiration date is applied.
  - Epicel grafts are delivered in a disposable shipper with vacuum insulated panels.
  - 3 self-sealing pouches are packaged in the inner container each containing 24 graft dishes (depending on the number of grafts ordered, empty dishes may be packed to prevent shifting during shipping).
- The Vericel representative will need a sturdy table, drape, gloves, and biohazard waste disposal. Please note: Epicel graft dishes cannot go on the sterile field.

Disposable shipper with vacuum insulated panels

Vericel provides a blood collection kit for a baseline blood sample:

- To be collected prior to graft placement for first procedure only.
- The Vericel representative will bring the kit and will package for shipping once the baseline blood sample is obtained.

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Recommended surgical supplies for Epicel grafting

- [ ] Smooth-edged pick-ups; recommend 2 per HCP
- [ ] Sterile normal saline
- [ ] Non-CHG patient prep cleanser, such as Betadine®, Vashe®, or Puracyn®
- [ ] Non-medicated scrub brush
- [ ] Bulb syringe or spray bottle
- [ ] Lap sponges
- [ ] Sterile specimen container for tissue sample or punch biopsy for quantitative wound culture, or wound swab culture for culture and sensitivity for bacteria and fungals
- [ ] Skin Graft Mesher (4:1 and 6:1 for autograft when used as an underlying mesh)
- [ ] Topical epinephrine or topical thrombin spray
- [ ] Staplers
- [ ] Fibrin sealant (preferably a slow setting type and mixture diluted per manufacturers' instructions)
- [ ] Inner dressings: sterilized bridal veil/nylon net/wound veil (e.g. DryVeil Contact layer)
- [ ] Outer dressings: soft absorbent burn gauze dressings
- [ ] Final outer bulky dressing for protection against shearing
- [ ] Appropriate antimicrobial solution, if required after grafting
- [ ] Stretch Net™ Tubular Elastic Dressing
- [ ] For Vericel representative: sterile gloves, basin, sturdy four-legged table without rim, towels, biohazard waste disposal

Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Patient information supplied by attending burn teams from 1989 to 1996 reported the adverse events of highest incidence as: death (13%), infection (13.8%), graft tear (7.8%) or graft blister (4.2%) and drainage (3.3%). Some of these events may have been due to the underlying burn injury and not the device itself.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Epicel underlay options

Epicel can be used in combination with a variety of underlay options. An appropriate underlay can provide a substrate and structure for Epicel grafts to improve take rate. **Please discuss the planning and staging of underlay options with your Vericel representative.**

Allograft

Allodermis technique retains the allograft dermis, or "allodermis", to serve as a substrate for Epicel.

Promotes rapid stratification, maturation and integration of Epicel, and the synthesis of anchoring fibrils. [6,13]

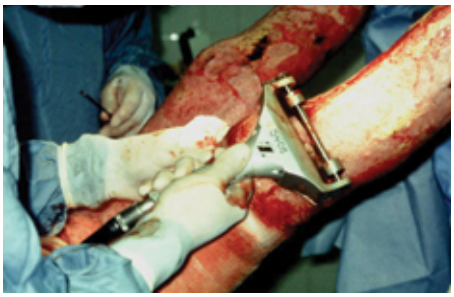
Autograft

Wide mesh autograft provides native cell signaling between the patient's dermis and Epicel.

Autograft meshed at a 4:1 or 6:1 ratio can be utilized as an underlay to provide structure for Epicel grafts.[2]

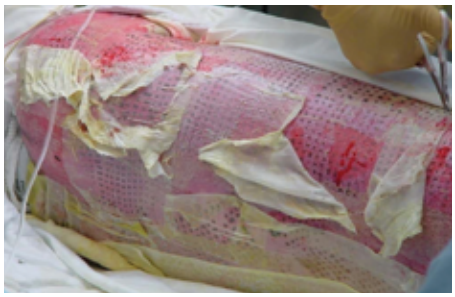
MEEK micrografting creates autograft "islands" allowing skin to grow from the margins.

MEEK micrografting can be used with higher autograft expansion ratios, up to 9:1, allowing for smaller donor sites.



Allodermis technique

Wide mesh autograft[2]



MEEK micrografting

Autograft donor site		
	Available	**Wide mesh autograft** (4:1, 6:1) or **MEEK micrografting** (9:1) can serve as an underlay for Epicel grafts
	Unavailable	**Engrafted allograft dermis** can serve as an underlay for Epicel grafts[5]

Epicel® (cultured epidermal autografts)

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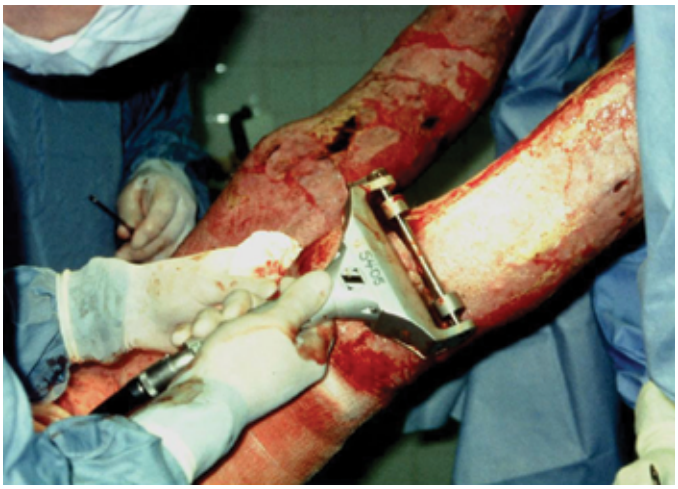
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Epicel grafting: allodermis technique

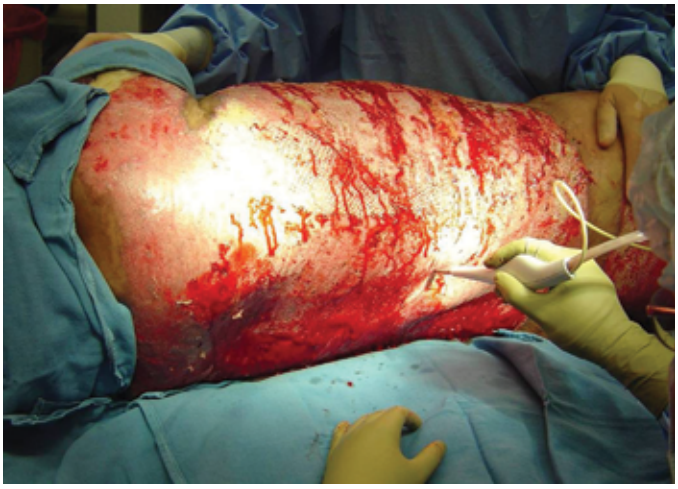
When autograft donor site is unavailable, engrafted dermis can serve as a substrate for the Epicel grafts

- The allograft epidermis is removed by dermabrasion prior to placement of Epicel. The allograft dermis, or "allodermis", is retained and serves as an excellent substrate, promoting rapid stratification, maturation and integration of Epicel, and the synthesis of anchoring fibrils.[6,13]

- Cuono et. al.[5] demonstrated much better results could be achieved with cultured epidermal autografts by employing a technique in which Epicel was placed on allodermis from cadaver allograft.[5,6]
  - If allograft has engrafted and the alloepidermis sloughs away prior to Epicel delivery, sterile normal saline dressings can be applied.



Epidermal layer of allograft is removed using a dermatome



Epidermal layer of allograft is removed using Versajet™

Epicel® (cultured epidermal autografts)

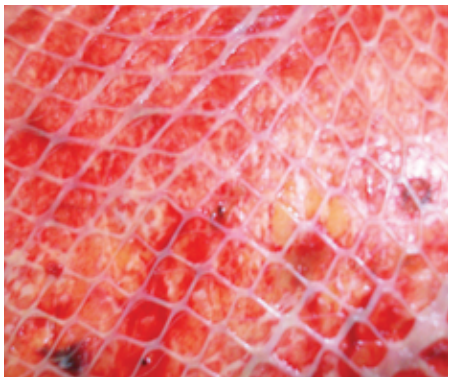
IMPORTANT SAFETY INFORMATION: Epicel is contraindicated in patients with a history of anaphylaxis following exposure to vancomycin, amikacin, and amphotericin, as trace quantities of these anti-infective agents may remain in the Epicel autograft. Epicel should not be used in patients with known sensitivities to materials of bovine or murine origin. It is contraindicated for use on clinically infected wounds.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

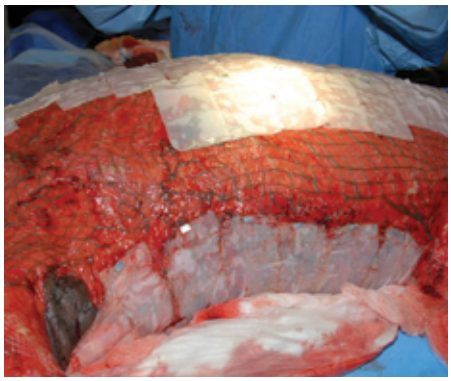
Epicel grafting: autograft technique

Wide mesh autograft

- Use of wide mesh autograft has advantages as a scaffold for Epicel.[5,13]
  - Meshed autograft placed under Epicel has proven to be effective. Autograft is meshed at a ratio of 4:1 or 6:1 and placed just prior to the placement of Epicel.[2]
  - Wide mesh autograft is utilized as an underlay to provide structure and native cell signaling between the patient's dermis and Epicel. Native cell signaling may promote healing.
- Once the wide mesh autograft is placed, a fine mist of fibrin sealant is sprayed, and the Epicel grafts are quickly applied.
  - Healing occurs as the spaces between the meshed autograft, or "interstices", fill in with the cultured epidermis
  - The underlying mesh increases the initial durability of Epicel.
  - Donor sites may also be covered with Epicel.
- Consider the availability of autograft to determine its placement over joints in order to minimize the occurrence of contracture.
  - If autograft is limited, it is recommended to prioritize autograft meshed at a ratio of 4:1 or 6:1 over joints as a scaffold for Epicel.
  - If autograft is sufficient, consider using autograft meshed at a ratio of 2:1 or 3:1 alone over joints to minimize joint contracture.



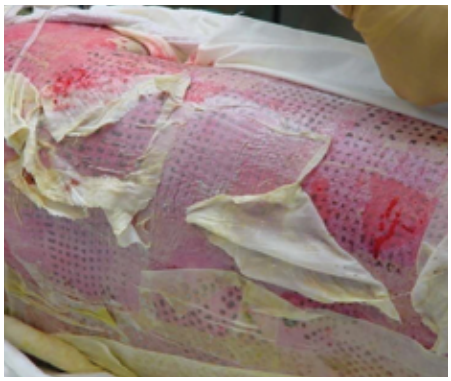
Wide mesh autograft[2]



Epicel is applied over widely meshed autograft[2]

MEEK micrografting

- The MEEK micrografting technique creates autograft "islands" allowing skin to grow from the margins.
  - The MEEK micrografting technique can be used with higher autograft expansion ratios, up to 9:1, allowing for smaller donor sites.
  - Epicel grafts are placed after the MEEK takedown procedure.



MEEK micrografting

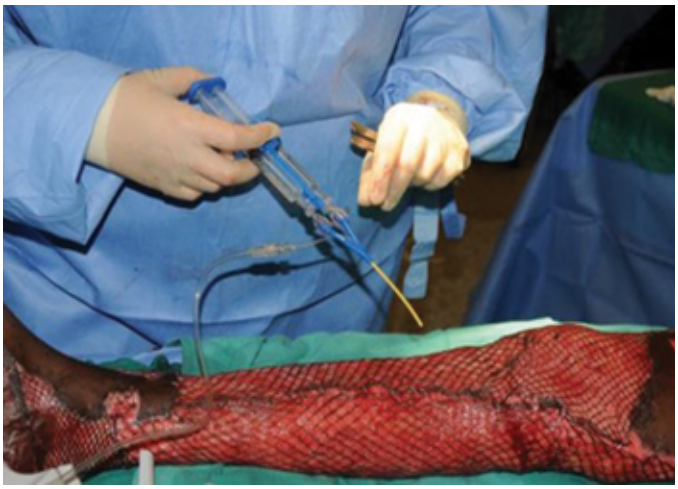
Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Because Epicel is manufactured with and contains residual amounts of murine cells, FDA considers it a xenotransplantation product. Therefore, recipients should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans because there is a potential risk of carrying an infection that is transmitted from mouse cells to humans.

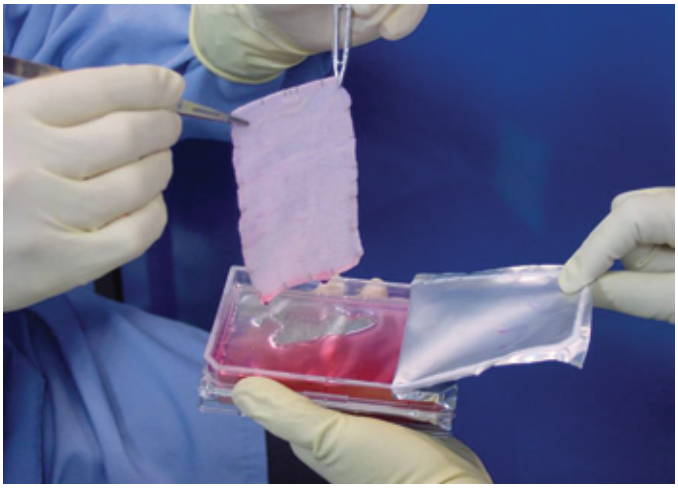
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Intraoperative Epicel grafting

- Reassess and prepare dermal wound bed.
- Collect wound cultures and baseline blood sample (note: a baseline blood sample is only collected at time of first Epicel grafting).
- Autograft donor sites can be harvested first, and wide mesh split-thickness autograft is placed just prior to placement of Epicel grafts.
- A fine mist of commercially prepared fibrin sealant may be applied immediately prior to laying the Epicel grafts, providing a full interface of cells against the wound bed.
  - It is important the fibrin sealant be applied in stages and to an area that will allow the Epicel grafts (approximately 6-8) to be readily applied prior to the set-up of the sealant.
- Once the Epicel graft dish is opened, the HCP must work within the dish and not touch the outside edges.
  - Smooth-edged pick-ups should be used rather than toothed pick-ups to prevent any tearing of the graft.
- Epicel grafts should be placed with cell sheet facing down on the wound bed and the petrolatum gauze backing facing up (the silver orientation tag on the back of the petrolatum gauze should be facing up).
- During the grafting procedure, open each Epicel graft dish only when the graft is ready to be applied.



Fibrin sealant being applied over wide mesh autograft prior to placement of Epicel grafts



Smooth-edged pick-ups being used to lift and place the Epicel grafts

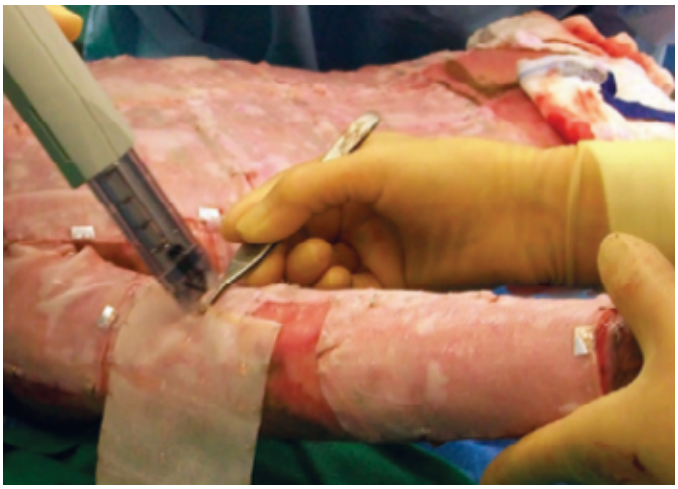
Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Squamous cell carcinoma (SCC) has been reported in patients with burn injury after being grafted with Epicel. Although SCC is a known complication of burn scars, the role of Epicel in the causation of SCC cannot be excluded.

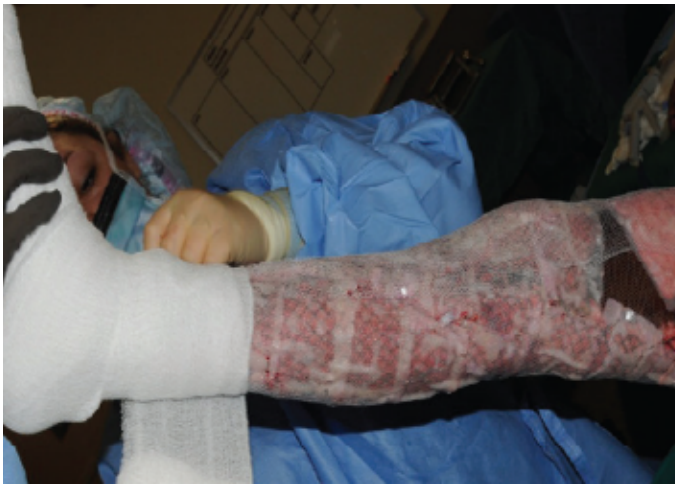
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Intraoperative Epicel grafting

- Epicel grafts should be placed as close together as possible with little to no overlap.
- Do not allow Epicel grafts to dry before they are applied to the wound bed.
- Handling of Epicel grafts should be kept to a minimum as it may cause a measurable reduction in cell viability.
- Epicel grafts should not be moved across the surface of the wound bed once it is applied as cell damage may result.
- If a delay occurs during Epicel graft placement, the inner shipping container holding the graft dishes should be resealed until grafting resumes.
- Once Epicel grafts have been applied, staple directly to the wound bed.
  - Staple adjacent grafts together. To prevent buckling, do not just staple the corners of the grafts.
- Epicel grafts can then be covered with sterile nylon net and secondary outer surgical dressings.
  - Sterile nylon net should be stretched tightly over the gauze backing. To secure the sterile nylon net, roll or hem at the edge and then staple.
  - Place 4-5 layers of absorbent gauze.
  - If topicals are applied, use the "wring-out" procedure, do not saturate.
  - Place bulky dressing as final outer layer.



Epicel grafts are applied cell-side down/silver tag up with little to no overlap before being stapled to adjoining grafts



Epicel grafts are covered with sterile nylon net and secondary outer surgical dressings

Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: The Epicel product is intended solely for autologous use. Patients undergoing the surgical procedure associated with Epicel are not routinely tested for transmissible infectious diseases. Discontinue use if the patient shows evidence of allergic reaction.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Tips for placement and handling of Epicel grafts

1. Place Epicel over wide mesh autograft or over MEEK micrografting (immediately after MEEK takedown of backing).

2. A fine mist of commercially prepared fibrin sealant may be applied immediately prior to laying the Epicel grafts, providing a full interface of cells against the wound bed.

   It is important the fibrin sealant be applied in stages and to an area that will allow the Epicel grafts (approximately 6-8) to be readily applied prior to the set-up of the sealant. Please refer to the directions for use from the product's manufacturer to determine how quickly the fibrin sealant product will "set-up."

3. During the grafting procedure, do not allow the grafts to dry before they are applied to the wound bed. Each graft dish should be opened only when the graft is ready to be applied.

4. Epicel grafts should be placed with cell sheet facing down on the wound bed and the petrolatum gauze backing facing up.

   The silver orientation tag on the back of the petrolatum gauze should be facing up.

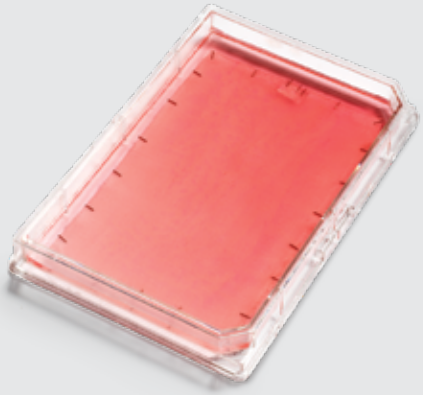
5. Handling of the grafts should be kept to a minimum as it may cause a measurable reduction in cell viability.

6. The graft should not be moved across the surface of the wound bed once it is applied as cell damage may result.

7. Grafts should be placed as close together as possible with little to no overlap.

8. Once grafts have been applied they are stapled directly to the wound bed.

9. Epicel grafts are then covered with an initial surgical dressing of sterile nylon net and secondary outer surgical dressings.



Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: If clinical signs of infection are present or develop, do not apply Epicel until the infection is adequately treated. The effectiveness of Epicel has not been proven in clinical studies. The long-term safety of Epicel is unknown. Over the past 27 years, the mortality from all causes was 13% before hospital discharge.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Epicel®
(cultured epidermal autografts)

Postgrafting

IMPORTANT SAFETY INFORMATION: Men and women who intend to have children should be advised that the effects, if any, of Epicel on fetal development have not been assessed. In addition, the safety of Epicel has not been studied in pregnant and nursing women.

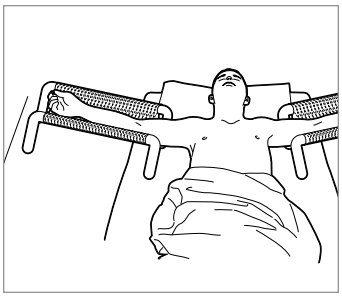
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

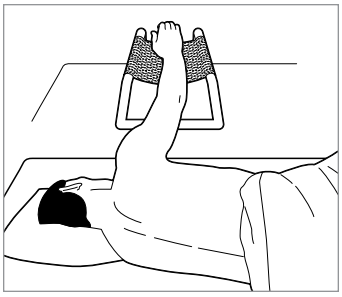
Postoperative patient care and positioning

- Drying of Epicel grafted areas is critical to support patient healing.
- Expose Epicel grafted areas to air at least 4 hours per day, preferably up to 12 hours, as tolerated. Exposing grafted areas to air helps dry out the grafts, which facilitates takedown of the graft backing.
- Dressing changes may need to be done in stages to best accommodate patient positioning.
- Patients with posterior grafts should be log rolled and extremities elevated to allow posterior surfaces to air dry (see images below).
- Avoid pressure and shearing of Epicel grafts.
- Use careful hand placement when positioning.
- Depending on graft placement and the patient, heavy padding, splinting or chemical paralysis may be appropriate.

Elevation techniques for drying of Epicel grafts

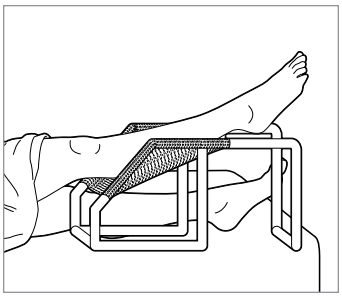
ARM ELEVATION

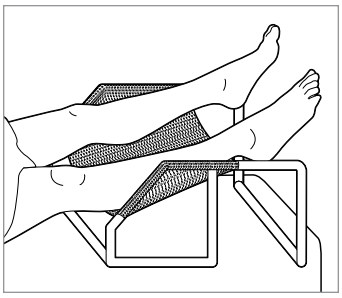




Patient is positioned on back with one or both arms outstretched or on their side with a single arm outstretched, also exposing patient's back for posterior drying

LEG ELEVATION





Patient is positioned on their back with one or both legs elevated for circumferential drying

Epicel® (cultured epidermal autografts)

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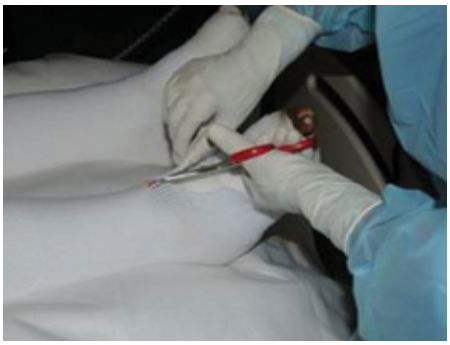
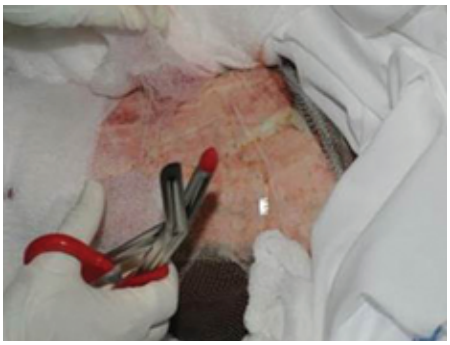
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Postoperative care and monitoring

- Change outer layers of dressing down to the bridal veil daily or more frequently if clinically indicated.
- Monitor Epicel grafted areas for signs of infection. Ensure there is no fluid build up underneath the graft.
- Obtain wound cultures as needed. If cultures show levels of bacteria 10^3, fungi, yeast, or colonization, topical antibiotics and/or antifungals may be effective.
- If topicals are applied, use the "**wring-out**" procedure, **do not saturate**.
  - Apply over the sterile nylon net, maximum of twice daily to prevent maceration of the grafts.
- Evaluate grafts at 3-5 days postop to plan timing of takedown.
  - May need window backing to assess wound bed.
- Do not use CHG/cytotoxic agents on or near body sites where Epicel grafts have been placed.
- No PT/OT to areas grafted with Epicel until takedown.
- Traffic in room should be limited and signage should be placed to indicate the need for PPE.



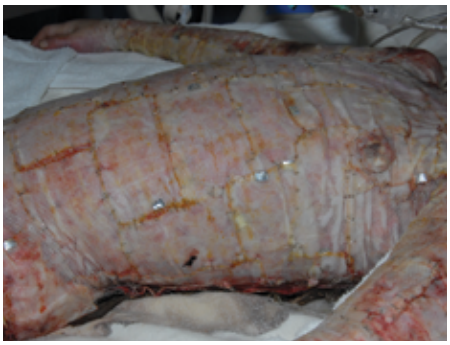
Changing outer layers of dressing



Dressing taken down to sterile nylon net

NO CYTOTOXIC AGENTS

Do not use any product containing chlorhexidine gluconate (CHG)



Exposed inner surgical dressing

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Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Timing and evaluation of takedown

The decision to proceed with takedown is based on appearance of gauze backings:

- If appearance is dry ("potato chip" appearance) and no evidence of infection, consider takedown at day 7-10.
- In the case of suspicious wound exudate, or if high levels of bacterial or fungal colonization are present under the graft (i.e. purulence), consider immediate takedown.
- Takedown can be performed either bedside or in the OR.

Evaluate at several sites on postop days 3-5:

- If sites appear wet, window sterile nylon net and gauze backing at 1-2 sites, evaluate exposed wound bed appearance over 10-15 minutes, then evaluate and culture.

After evaluation, if grafts appear:

- **Good:** Epicel is pink and shiny with a confluent appearance

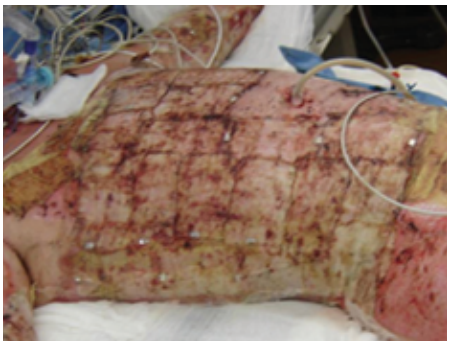
  HOLD TAKEDOWN, RESUME DAILY DRESSING CHANGES AND DRYING REGIMEN TO POD 7-10

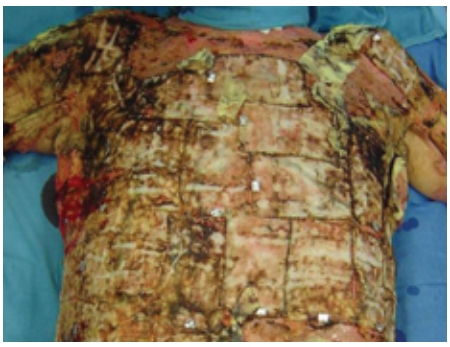
- **Questionable:** Epicel has a raw/bloody appearance

  RESUME DAILY DRESSING CHANGES/DRYING REGIMEN AND THEN RE-ASSESS, RECHECK IN 2 DAYS

- **Poor:** Wound bed shows purulence and/or maceration

  IMMEDIATE TAKEDOWN AND INITIATE TOPICAL ANTIMICROBIAL TREATMENT TO AFFECTED AREAS





Normal appearance of Epicel graft backings prior to takedown

Please consult your Vericel representative regarding early or delayed takedown procedure.

Epicel® (cultured epidermal autografts)

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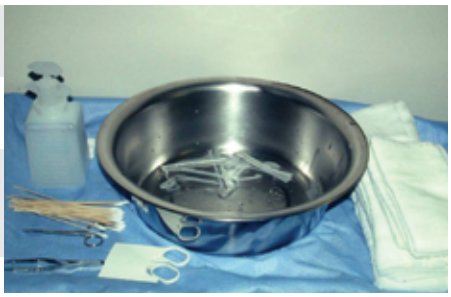
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Recommended supplies for takedown

- [ ] Smooth-edged pick-ups
- [ ] Sterile normal saline
- [ ] Sterile poloxamer, noncytotoxic wound cleanser (e.g. PrimaDerm® or Prontosan®)
- [ ] Staple removers
- [ ] Sterile cotton-tipped applicators
- [ ] Bandage scissors
- [ ] Wound swab culture for culture and sensitivity for bacteria and fungals
- [ ] Bulb syringe or spray bottle
- [ ] Inner dressings: must be nonadherent (e.g. Adaptic® or Cuticerin™)
- [ ] Outer dressings: soft absorbent burn gauze dressings
- [ ] Appropriate antimicrobial topical solution (if required after takedown)
- [ ] Final outer bulky dressing for protection against shearing (if needed)



Supplies needed for graft takedown

Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Because Epicel is manufactured with and contains residual amounts of murine cells, FDA considers it a xenotransplantation product. Therefore, recipients should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans because there is a potential risk of carrying an infection that is transmitted from mouse cells to humans.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Takedown of Epicel: presoaking

- Presoaking gauze should be started approximately 12 hours prior to scheduled takedown and repeated every 4 hours.
- Presoaking can aid in the atraumatic removal of gauze backings.
- Once presoaked, backings should easily be lifted off with no bleeding.
- Surfactants aid in releasing the backing from the skin. Surfactants include: PrimaDerm®, Prontosan®, or baby shampoo.
- The presoak liquid can be saline or 1L saline + 2 bottles surfactant (e.g. PrimaDerm or Prontosan).
- Baby shampoo can be used as an aid during the takedown procedure but should not be used in the presoak liquid.

Steps in takedown of Epicel

1. **Remove staples** from the sterile nylon net and carefully remove.

2. **Remove the staples used to affix the petrolatum gauze**. Gently peel the gauze backing down and away from the wound bed; do not pull up on the gauze backing.

   Sterile cotton-tipped applicators may help "tease" the gauze backing from the cultured epidermis if it lifts from the wound bed. If after soaking with sterile saline or sterile poloxamer, noncytotoxic wound cleanser (100 mL per 0.5L NSS) the gauze backings still adhere, the takedown procedure should be delayed. In this case, replace the outer dressing and heavily soak with sterile poloxamer, noncytotoxic wound cleanser overnight.

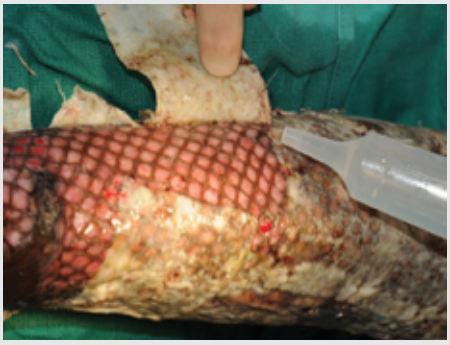
3. **Wound cultures of the cultured epidermis** should be obtained along with sensitivities for bacterial and fungal organisms.

4. **Apply nonadherent dressings** to all areas of cultured epidermis (e.g. Adaptic® or Cuticerin™).

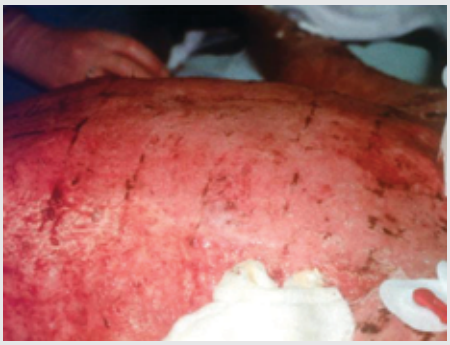
5. **A soft, absorbent sterile gauze wrap** is applied as an outer layer over the non-adherent dressing.

   If no drainage or infection is present, a dry dressing is applied; if topicals are applied, use the "wring-out" procedure, do not saturate.

To help release gauze backing, discuss a pre-soak with medical team using either saline or sterile poloxamer, noncytotoxic wound cleanser (e.g. PrimaDerm® or Prontosan®) every 4 hours the night prior to takedown.



Irrigation may help to release the gauze backing



Exposed new skin

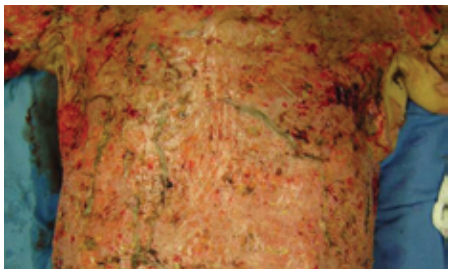
Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: The Epicel product is intended solely for autologous use. Patients undergoing the surgical procedure associated with Epicel are not routinely tested for transmissible infectious diseases. Discontinue use if the patient shows evidence of allergic reaction.

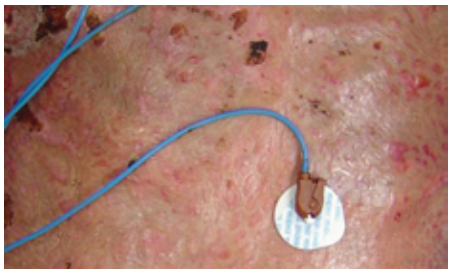
Postoperative care after takedown

It is critical to monitor Epicel grafted areas closely.

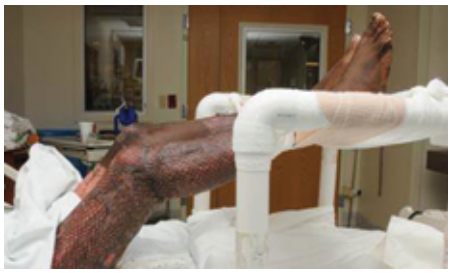
- Outer and inner non-adherent dressings need to be changed daily to expose new skin to air.
  - If dressing adheres, irrigate and tease away to avoid pulling and shearing.
- Continue to expose grafted areas to air at least 4 hours per day, preferably longer up to 12 hours as tolerated.
- Monitor daily for signs of infection (drainage or odor), continue wound cultures as needed.
- Apply non-adherent dressing (e.g. Adaptic® or Cuticerin™) directly over Epicel then apply outer gauze wrap.
- If topicals are applied, use the "**wring-out**" procedure, **do not saturate**.
- Gentle PT/OT may be initiated with dressings off. Be careful with hand placement during range of motion (ROM) exercises.
- The following activities should be performed with dressings:
  - Patient can be lifted to a recliner.
  - Ambulation should be delayed and re-evaluated approximately 3 days after takedown.
- ACE® wraps should be utilized for lower-extremity venous support for dependent activities.
- Continue to avoid shearing forces.
- Do not use CHG/cytotoxic agents on or near body sites where Epicel grafts have been placed.
- Do not soak or scrub Epicel grafted areas.



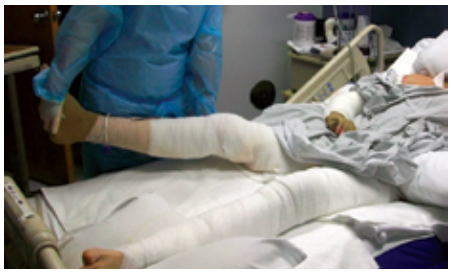
Epicel grafts are fragile in the initial stages after takedown



Epicel grafts in the initial stage after takedown



PVC bridge for gentle elevation and drying of Epicel-treated areas



Therapist with patient

Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: If clinical signs of infection are present or develop, do not apply Epicel until the infection is adequately treated. The effectiveness of Epicel has not been proven in clinical studies. The long-term safety of Epicel is unknown. Over the past 27 years, the mortality from all causes was 13% before hospital discharge.

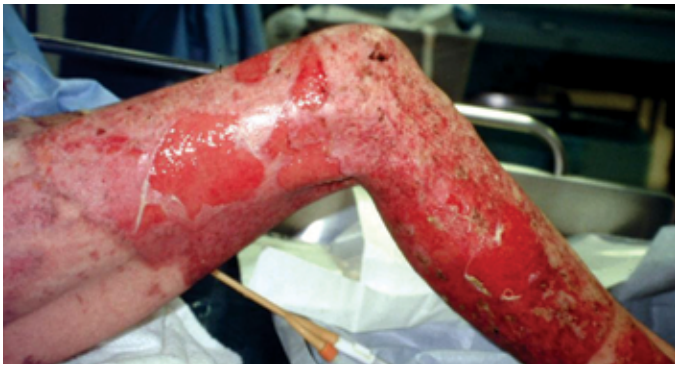
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Shearing

- **Shearing can primarily occur at two stages:** immediately after grafting (POD 1-7) and following takedown procedure (POD 10-21+).
- **To help prevent shearing:**
  - Use extra outer dressings to pad areas of potential compromise.
  - Carefully manage patient movement, limit ROM.
  - Obtain additional lifting help and use careful hand positioning during dressing changes, patient re-positioning and linen changes.
  - When gentle ROM is initiated after takedown, conduct therapy with dressings off.
  - Convey graft fragility to burn team in notes and via signage.
  - Limit amount of contact with the patient until necessary.
- **If shearing occurs:**
  - Apply light, non-adherent dressings and antibiotic ointment as needed and appropriate.
  - Monitor closely with dressing changes daily or every other day until healed.

Blistering

- **For small and uninfected blisters** (less than $2cm^2$) monitor only.
- **For larger or compromising blisters** such as over a joint, or for blisters appearing infected:
  - Gently express liquid (consider careful needle aspiration to minimize disturbing new epithelium).
  - Apply light, non-adherent dressings and antibiotic ointment as needed and appropriate.
  - Monitor closely with dressing changes daily or every other day until healed.
- **For blisters resulting from friction:**
  - Minimize at source via modified splints or alter patient activities to minimize rubbing motion.
  - If wearing pressure garments, temporarily discontinue.



It is important to communicate the need for gentle handling of the Epicel grafted areas to those responsible for care of the patient.

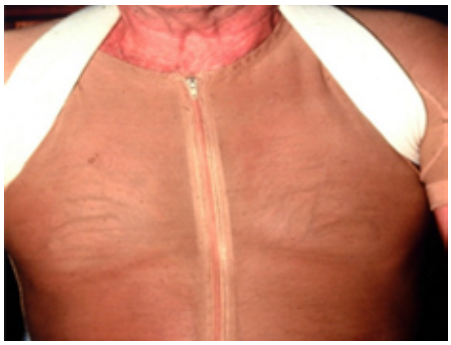
Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Men and women who intend to have children should be advised that the effects, if any, of Epicel on fetal development have not been assessed. In addition, the safety of Epicel has not been studied in pregnant and nursing women.

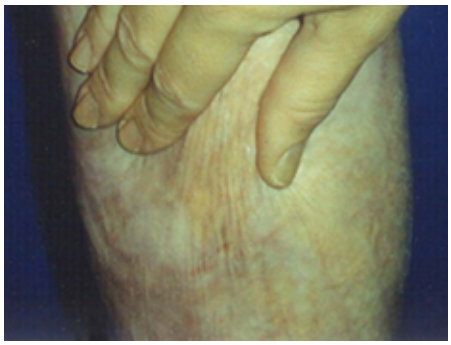
Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Intermediate to long-term care considerations

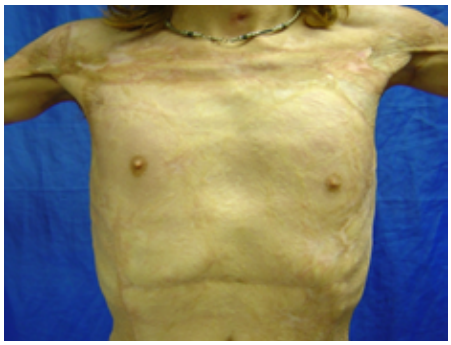
- Wash with mild soap (gentle, non-irritating, non-perfumed). Avoid tub immersion and soaking to prevent skin maceration.
  - Once grafts are fully confluent, patient may shower—approximately 4-6 weeks after graft placement.
- Moisturize with mild lotion or cream (water based preferred, non-perfumed, non-irritating).
- Monitor and treat blisters conservatively in Epicel grafted areas; apply light dressing as indicated.
- Apply pressure garments (per physician protocol) when wounds are closed.
  - Approximately 6 weeks after graft placement, zippered garments recommended.
  - Consider using soft liner inserts over fragile areas and joints to prevent disruption of the epidermis.
- Increase activity levels as patient tolerates.
- Avoid sun exposure to grafted areas and apply sunscreen.



Pressure garment over Epicel-treated areas



Healed Epicel grafts on lower leg



Epicel-treated patient 12+ months after surgery

Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: Patient information supplied by attending burn teams from 1989 to 1996 reported the adverse events of highest incidence as: death (13%), infection (13.8%), graft tear (7.8%) or graft blister (4.2%) and drainage (3.3%). Some of these events may have been due to the underlying burn injury and not the device itself.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

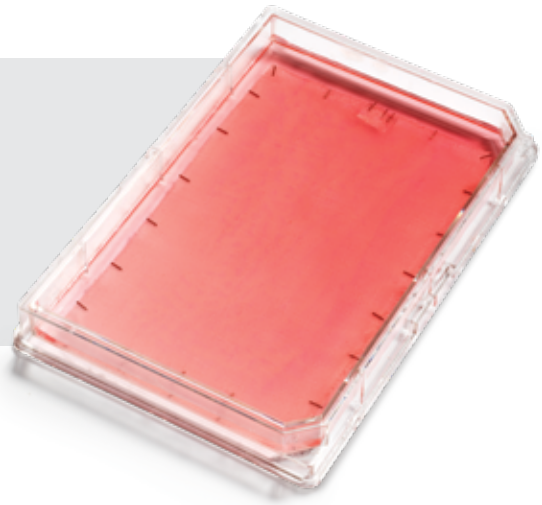
Adverse event reporting

An adverse event is any undesirable experience associated with the use of a medical product in a patient. It is Vericel's policy to comply with all regulations and laws relating to reporting adverse events, other safety findings, medical device reports and product complaints.

Vericel is committed to patient safety. Part of our mission to serve patients includes collecting, reviewing and reporting all adverse events, other safety findings, medical device reports and product complaint information associated with the use of Vericel's investigational and marketed products.

To report an adverse event, medical device report, other safety finding, or product complaint:

Call: 1-800-453-6948
Email: PatientSafety@vcel.com



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Epicel® (cultured epidermal autografts)

IMPORTANT SAFETY INFORMATION: From June 1998 through September 2015 adverse events received by Genzyme Biosurgery (predecessor in interest to Vericel) and Vericel Corporation were similar to the previously identified adverse events. Events that were reported in ≥ 1% of patients included multi-organ failure (6.6%), sepsis (5.2%) infection (4%) and skin graft failure/graft complication (2.7%). The relationship of these events to Epicel has not been established.

Please see Important Safety Information. For more information, see Epicel Instructions for Use and Patient Information.

Epicel®
(cultured epidermal autografts)

Permanent skin covering for burns 30%+ TBSA

Epicel patient survival

In the Epicel Clinical Experience databases (1989-2015), 954 adult and pediatric patients with a mean TBSA of 67.3% showed **84.4%** survival.[14]

The overall survival rate was **84.4%** (804/954) at hospital discharge. The survival rate for pediatric patients was **88.9%** and for adults the survival rate was **82.0%**.[14]

Burn patient survival

In the 2016 National Burn Repository, 8,870 burn patients with a TBSA of 30%-90% showed:

68.0%
survival[15]

Specialists are available to answer reimbursement questions about Epicel and the CEA procedure at:

1-800-CEA-SKIN (1-800-232-7546)

support@epicelaccess.com

Please see Important Safety Information.
For more information, see Epicel Instructions for Use and Patient Information.

VERICEL® Burn Care

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