Epicel®
(cultured epidermal autografts)
HDE# BH990200

Instructions for Use

HUMANITARIAN DEVICE: Authorized by Federal law 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%. **Epicel®** 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.

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

DESCRIPTION

Epicel® (cultured epidermal autografts) is an aseptically processed wound dressing composed of the patient's own (autologous) keratinocytes grown ex vivo in the presence of proliferation-arrested, murine (mouse) fibroblasts. Epicel consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick and is referred to as a cultured epidermal autograft. Each graft of Epicel is attached to petrolatum gauze backing with titanium surgical clips and measures a minimum of 50 cm^2 in area.

Epicel is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation and the FDA *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* as a xenotransplantation product because it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3, fibroblast feeder cells. Please refer to the FDA xenotransplantation page for these guidelines and further xenotransplantation information: https://www.fda.gov/vaccines-blood-biologics/xenotransplantation. For recommendations regarding Epicel recipient blood and tissue donation, please refer to the Patient Counseling section.

The mouse 3T3 cells have been extensively tested for the presence of infectious agents. Those tests include sterility testing for bacterial and fungal contamination, testing for mycoplasma contamination, and screening for viral and retroviral contaminants. Additional evaluations regarding the proliferative potential of the mouse 3T3 cells, their potential to undergo transformation and their karyology have been conducted. Epicel is evaluated for contamination via a pre-release sterility test followed by a standard 14-day sterility test, post-release. Reagents used in the manufacture of Epicel are tested for sterility and endotoxin content. The manufacturing process is periodically monitored for the possibility of mycoplasma contamination. Product manufacture includes reagents derived from U.S. herd animal sources that are tested for sterility and viruses. Patients and the biopsy tissue (autologous cells) harvested from them (to manufacture Epicel) are not routinely tested for transmissible infectious agents.

INDICATIONS FOR USE

Epicel® is indicated 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.

CONTRAINDICATIONS

Do not use in patients with a history of hypersensitivity following exposure to vancomycin, amikacin, or amphotericin, as trace quantities of these anti-infective agents may remain in the Epicel® autograft.

Do not use in patients with sensitivities to materials of bovine or murine origin. The cell culture medium used in the culture of Epicel contains bovine serum and the cells are co-cultured with murine 3T3 fibroblasts. The medium used to package and transport Epicel does not contain serum; however, trace quantities of bovine-derived proteins may be present (see the How Supplied section for a listing of manufacturing reagents).

Do not use on clinically infected wounds (see also Precautions).

WARNINGS

Hypersensitivity Reactions

Do not continue to graft patients with Epicel® if the patient shows evidence of an allergic reaction. Allergic reactions or hypersensitivity reactions may manifest themselves as classical Type I-IV immune responses, e.g., anaphylaxis, hemolysis, antigen/antibody complex formation or a cell-mediated/delayed immune response.

Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma (SCC) has been reported in patients with burn injury after being grafted with Epicel. Distinctive features of these cases include multicentric location, large size, aggressive growth, local recurrence after resection, and fatal outcome in some of the cases. In the reported cases, the SCC occurred in the grafted areas 11 to 23 years after Epicel grafting. A latency period of 11 to 41 years (median 28) based on a systematic review of case series published in 2000 or later from the time of burn injuries to occurrence of SCC is reported in the literature.[1,2]

A patient with epidermolysis bullosa dystrophica (DEB) developed an invasive SCC a few days after grafting with Epicel. The patient underwent a lower extremity amputation within weeks of diagnosis.

Of the seven patients diagnosed with SCC with known age, one was an eight-year-old child at the time of treatment with Epicel. The child was diagnosed with SCC in the area of the Epicel graft 11 years and 7 months after treatment, and the outcome was fatal.

Although SCC is a known complication of burn scars and DEB, the role of Epicel in the causation of SCC cannot be excluded.

Blood and Organ Donations

Epicel 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 Epicel is manufactured by co-cultivation with murine cells and contains residual murine cells; therefore, it is a xenotransplantation product (see Description).

Infectious Agent Transmissions

Health care providers should employ universal precautions in handling the biopsy samples and the Epicel product. Patients undergoing the surgical procedure associated with Epicel are not routinely tested for transmissible infectious diseases. Therefore, the Epicel biopsy and the autologous Epicel product may carry the risk of transmitting infectious diseases to health care providers handling these tissues.

PRECAUTIONS

Agents Harmful to Epicel

Do not use cytotoxic agents with Epicel®. Do not use products containing chlorhexidine gluconate (such as Hibiclens®) to treat wound bed infections in patients who have received or are expected to receive Epicel. Please refer to a list of anti-infective agents in the Pre-Grafting Considerations section in the Instructions for Use. These are agents that have been used clinically and have not been observed to cause significant inhibitory effects on keratinocytes in vitro, or for which limited clinical experience has been obtained.

Wound Bed Infection

If clinical signs of infection (pain, edema, erythema, warmth, drainage, odor or unexplained fever) are present or developing, do not apply Epicel until the infection is adequately treated. Epicel is more susceptible to wound bed conditions and bacterial colonization, compared to meshed split-thickness autografts. All infections should be evaluated and treated according to standard clinical practice.

Potential Infection from Murine Cells

Although the murine cells used in the manufacture of Epicel have been tested and found to have no detectable bacteria, fungi and viruses, the possibility of Epicel containing an infectious agent(s) cannot be excluded. The risk of infection transmitted by Epicel is unknown. It is also possible that symptoms or signs of an infection transmitted by Epicel may not be reported or seen for months or years. To date, Vericel is not aware of any infections related to murine cells.

Impairment of Fertility – Pregnancy – Nursing Mothers

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.

ADVERSE REACTIONS

The mortality from all causes was 13% before hospital discharge.

The most common adverse reactions, occurring in ≥2% of patients with deep dermal or full thickness burn injuries treated with Epicel® were infection, graft shear, blister, drainage, sepsis, graft detachment, and renal failure.

Epicel Clinical Experience

Because data are collected under widely varying conditions, adverse reactions observed for Epicel cannot be directly compared to rates in the clinical trials of another device and may not reflect the rates observed in practice.

The overall safety information for Epicel is derived from two Epicel safety databases, comprised of pediatric and adult patients who received Epicel treatment. The data are summarized in Table 1 and Table 2.

Table 1 (1989-1996, n=552) includes 205 children (aged 21 years and younger, with 71% males) and 347 adults (mean age of 39 years with 76% males). The adverse reactions were collected from treating physicians or burn teams. Total number of deaths was 74 (13%).

Table 1: Adverse Reactions Reported in ≥1% of Patients with Deep Dermal or Full Thickness Burn Injuries (n = 552) Treated with Epicel 1989-1996

	Number of Patients (%)			Number of Adverse Reactions		
	Pediatric (n = 205)	**Adult (n = 347)**	**Total (n = 552)**	**Pediatric**	**Adult**	**Total**
Number of Patients with any AE n (%) and total number of AEs	94 (45.9%)	185 (53.3%)	279 (50.5%)	178	341	519
Colonization/Infection	31 (15.1%)	45 (13.0%)	76 (13.8%)	34	50	84
Graft Shear	11 (5.4%)	32 (9.2%)	43 (7.8%)	12	33	45
Blister	9 (4.4%)	14 (4.0%)	23 (4.2%)	10	15	25
Drainage, wet or macerated	8 (3.9%)	10 (2.9%)	18 (3.3%)	8	10	18
Cleaning damage or unclean bed	8 (3.9%)	9 (2.6%)	17 (3.1%)	8	9	17
Sepsis, Septic Shock	7 (3.4%)	10 (2.9%)	17 (3.1%)	7	10	17
Epicel Damage	6 (2.9%)	8 (2.3%)	14 (2.5%)	6	8	14
Graft Detachment	6 (2.9%)	8 (2.3%)	14 (2.5%)	6	8	14
Grafts Debrided with Dressing	2 (1.0%)	9 (2.6%)	11 (2.0%)	2	9	11
Renal Failure or Disorder	0	11 (3.2%)	11 (2.0%)	0	11	11
Wound heal impaired or slow	2 (1.0%)	5 (1.4%)	7 (1.3%)	3	5	8
Poor blood (platelets, RBCs)	1 (0.5%)	5 (1.4%)	6 (1.1%)	2	5	7

Table 1: Adverse Reactions Reported in ≥1% of Patients with Deep Dermal or Full Thickness Burn Injuries (n = 552) Treated with Epicel 1989-1996

	Number of Patients (%)			Number of Adverse Reactions		
	Pediatric (n = 205)	Adult (n = 347)	Total (n = 552)	Pediatric	Adult	Total
Multi-organ failure	1 (0.5%)	5 (1.4%)	6 (1.1%)	1	5	6
Pressure/friction on site	2 (1.0%)	4 (1.2%)	6 (1.1%)	2	4	6
Takedown improper	2 (1.0%)	4 (1.2%)	6 (1.1%)	2	4	6
Unfavorable topical agents	3 (1.5%)	3 (0.9%)	6 (1.1%)	3	3	6
Allergy, allergic reaction	2 (1.0%)	3 (0.9%)	5 (0.9%)	2	3	5
Decreased vascular flow	0	5 (1.4%)	5 (0.9%)	0	5	5
Blood pressure (low, high)	0	4 (1.2%)	4 (0.7%)	0	4	4
Hypothermia	0	4 (1.2%)	4 (0.7%)	0	4	4
Febrile, Fever	3 (1.5%)	0	3 (0.5%)	3	0	3
Contractures	3 (1.5%)	0	3 (0.5%)	3	0	3
Hematoma	2 (1.0%)	1 (0.3%)	3 (0.5%)	2	1	3
Movement/manipulation of graft	2 (1.0%)	0	2 (0.4%)	2	0	2

Table 2 (1998-2015, n=1662), which represents the number of devices from tracking/sales data, includes 589 children (aged 21 years and younger) and 1073 adults. The reporting sources for the adverse reactions include spontaneous reports via medical device reports, reports from burn sites, and published literature. Because of the potential underreporting of adverse reactions from these sources, the percentages of adverse reactions should be interpreted with caution. It is not always possible to estimate adverse reaction frequencies reliably or establish a causal relationship to device exposure. The total number of deaths was 147 (8.8%). The most common adverse reactions in ≥2% of patients were multi-organ failure, sepsis, infection, and graft procedure complications.

Table 2: Frequency of Spontaneous Reports of Adverse Reactions in ≥1% of Adult or Pediatric Patients with Deep Dermal and Full Thickness Burn Injuries (n = 1662) Treated with Epicel from June 24, 1998, to September 17, 2015

	Pediatric Cases n = 589	**Adult Cases n = 1073**
Multi-organ failure	14 (2.4%)	45 (4.2%)
Sepsis	8 (1.4%)	41 (3.8%)
Infections	12 (2%)	21 (2%)
Graft Procedure Complications	4 (0.7%)	21 (2%)
Respiratory Disorders	6 (1%)	16 (1.5%)
Cardiac arrest	2 (0.3%)	11 (1%)
Vascular Disorders	0	11 (1%)
Renal failure	0	11 (1%)

CLINICAL STUDIES

The probable benefit of Epicel®, mainly related to survival, was demonstrated in two Epicel databases and one physician-sponsored study, as shown in Table 3, Table 4, and Table 5.

Table 3 (1989-1996, n=552) includes 205 children (aged 21 years and younger with 71% males). Demographics, clinical outcome (survival), and adverse reactions (see Table 1) data were recorded for patients who received Epicel (mean number of grafts=104, range of 4-408) from 1989 to 1996. The survival rate for overall patients was 86.6% (478/552) at three months post-initial surgery. The survival rate was 89.3% (183/205) for pediatric patients (21 years and younger).

Table 3: Epicel Database (1989 – 1996): Demographics and Survival Data in Pediatric and Overall Population

	Overall		Pediatric patients	
	Total Treated Patients n	**Survived n (%)**	**Total Treated Patients n**	**Survived n (%)**
Number of Patients	552	478 (86.6)	205	183 (89.3)
Sex				
Male n (%)	409 (74.1)	355 (86.8)	145 (70.7)	132 (91.0)
Female n (%)	116 (21.0)	98 (84.5)	50 (24.4)	43 (86.0)
No Data n (%)	27 (4.9)	25 (92.6)	10 (4.9)	8 (80.0)
TBSA 3rd Degree Burn[1] (Mean % TBSA ± SD)	56.1 ± 21.2	54.4 ± 20.9	58.0 ± 21.7	55.8 ± 21.0
Mean TBSA[2] (% ± SD)	68.6 ± 17.4	67.6 ± 17.1	68.8 ± 17.3	67.5 ± 17.0
Inhalation Injury[3] n (%)	195 (35.3)	159 (81.5)	69 (33.7)	56 (81.2)

[1] 3rd Degree Burn: also referred to as full-thickness burns, are characterized by total irreversible destruction of all skin, dermal appendages, and epithelial elements. Spontaneous regeneration of epithelium is not possible.
[2] TBSA: Total Body Surface Area including third degree burn area.
[3] Based on available recorded information for "moderate" or "severe" inhalation injury.

Table 4 (October 2007-June 22, 2015, n=402) demonstrates Epicel tracking data as per FDA requirement following Epicel approval in 2007. Demographics and survival information have been collected under this database. During the period from October 2007 to June 2015, a total of 402 patients received Epicel in the US according to the labeled indication, with average age of 32 years; 73% were males, and the average burn size was 66% of TBSA. Of these 402, there were 120 pediatric patients with average age of 12 years; 71% were males, and the average burn size was 66% of TBSA. The survival rate in this pediatric population was 88.3% (106/120) as compared with the overall survival rate of 81.3% in the total population (327/402).

Table 4: Epicel Database (October 2007 to June 2015): Patient Demographics and Survival Data in Pediatric and Overall Population

	Overall		Pediatric Patients	
	Total Treated Patients n	**Survived n (%)**	**Total Treated Patients n**	**Survived n (%)**
Number of Patients	402	327 (81.3)	120	106 (88.3)
Sex				
Male n (%)	293 (72.9)	238 (81.2)	85 (70.8)	74 (87.1)
Female n (%)	101 (25.1)	81 (80.2)	32 (26.7)	29 (90.6)
No Data n (%)	8 (2.0)	-	3 (2.5)	-
Mean Age (yrs ± SD)	32.0 ± 17.1	-	12.2 ± 7.0	-
Mean TBSA[1] (% ± SD)	66.0 ± 17.6	-	66.4 ± 18.7	-

[1] TBSA: Total Body Surface Area including third degree burn area.

Table 5 summarizes published data from a randomized, controlled, independent, physician-sponsored study conducted by Dr. Andrew Munster. This study compared the outcome of therapy in patients with massive burns with or without cultured epidermal autografts (Epicel).[3] Two groups of patients were studied over a seven-year period. One group received standard care (excision plus allografting and/or split thickness autografting) and the other group received standard care plus Epicel. All patients in the study had to satisfy the following entry criteria: 1. a minimum burn size of 50% TBSA with a substantial third-degree component, and 2. survival beyond the first operative procedure for excision and initial coverage. The data from Table 5 were collected by Genzyme Biosurgery (previous owner of Epicel) from medical records of 44 patients in the study.

Table 5: Available Data from Munster Study

Parameter	Epicel	Control
Number of Patients (n)	20	24
Sex		
Male n (%)	15 (75.0)	22 (91.7)
Female n (%)	5 (25.0)	2 (8.3)
Mean 3rd Degree Burn (%)	41.4 ± 20.92	38 ± 25.37
Risk Factors		
Mean Age (yrs)	29.6 ± 13	44.0 ± 18.5
Mean TBSA (%)	69.1 ± 15.03	62.9 ± 13.16
Inhalation Injury n (%)	18 (90.0)	19 (79.2)
Final Status at 7 years		
Survival n (%)	18 (90.0)	9 (37.5)

HOW SUPPLIED/STORAGE AND HANDLING

Epicel® is intended solely for autologous use.

Epicel consists of viable, autologous cells packaged and labeled for use within specified time limits. Each Epicel graft consists of a sheet of cultured epidermal cells attached with titanium surgical clips to a backing of petrolatum gauze. The petrolatum gauze backing serves to support and protect the autograft during transport, the grafting procedure, and the early post-grafting period. Each graft is rectangular in shape and has a surface area of a minimum of 50 cm^2. A silver orientation tag is attached to the petrolatum gauze indicating that the gauze should be placed facing up.

Each graft is individually packaged in sterile, buffered, serum-free, unsupplemented Dulbecco's Modified Eagle Medium (DMEM) and shipped within secondary packaging capable of maintaining the appropriate storage temperature during transportation and handling. DMEM is a physiological nutrient-rich buffer medium primarily containing salts, amino acids, and vitamins, as well as phenol red. Its salt composition is very similar to human plasma salt composition and effectively maintains physiological osmolality. None of the components of DMEM are of animal origin.

The following components are used during the manufacture of Epicel: anti-infective agents such as vancomycin, amikacin or amphotericin B; bovine serum; culture media supplements such as insulin, triiodothyronine, hydrocortisone, cholera enterotoxin, and epidermal growth factor; and proliferation-arrested murine fibroblasts.

To maintain cell viability, Epicel is aseptically manufactured, but is not terminally sterilized. Epicel is shipped following a preliminary pre-release sterility test to confirm the absence of microbial growth. Final (14-day incubation) sterility test results are completed after the time of device application.

Storage and Handling in preparation for grafting

- Confirm that the patient's identity matches the patient identifiers on the Epicel labels.
- Do not use if patient's identity does not match the Epicel labeled patient identifiers.
- Inspect the Epicel packaging and ensure that it is intact.
- Do not use Epicel if package is opened or damaged.
- Store Epicel in the original shipping container in which it is received.
- Maintain the shipping carton closed and at cool room temperature (13°C to 23°C, 55°F to 73°F).
- Do not refrigerate, freeze, or incubate the Epicel shipping container or its contents.
- Do not remove from original shipping container until ready for use.
- Keep Epicel out of the operating room until ready for application.
- Do not reuse, freeze, refrigerate, or sterilize Epicel after opening.
- Inspect the self-seal bags that contain Epicel grafts for media leaks.
- If a self-seal bag contains media, then inspect each graft dish in the bag for broken seal or damage prior to use.
- Inspect the medium in which Epicel is transported.
- Do not use an Epicel graft if the medium appears cloudy, or the graft dish has a broken seal or is damaged.
- Do not use Epicel past its expiration date.

INSTRUCTIONS FOR USE

Pre-Grafting Considerations

The recipient wound bed may influence the success of keratinocyte graft application. Spontaneous blister formation may occur in patients grafted with keratinocytes alone and may result in graft loss. The use of a dermal substitute may improve final graft take, however the use of Epicel with dermal substitutes has not been studied.

The application of a dermal substitute should be conducted according to established, standard operating procedures. The wound must be clean, well vascularized and dry (nonexuding). If a dermal substitute such as cadaver allograft is being used, the epidermal layer must be removed from engrafted allograft prior to the application of Epicel®. Since this layer is very thin, care must be taken not to remove the engrafted dermis. The epidermal layer is generally removed with a dermatome, but the removal process should be determined by standard operating procedures within the burn unit.

The anatomic site intended for graft application may influence graft success. Mechanical stress may be one of the reasons for graft blister formation.

Epicel is more sensitive to wound bed conditions and colonization, compared to the sensitivity of meshed split-thickness grafts. *Staphylococcus, Pseudomonas,* and *Candida* have been shown to be particularly detrimental to the adherence and viability of cultured keratinocytes. *Acinetobacter, Enterococcus, Proteus, Serratia* and *Aspergillus* have also demonstrated detrimental effects on graft take.

Anti-infectives commonly used to treat wound bed infection vary widely in their effects on cultured keratinocytes. The optimal clinical use of systemic and/or topical antibiotic therapy before and after grafting has not been determined.

Agents that have been used clinically and have not demonstrated significant inhibitory effects on keratinocyte growth and differentiation in a cell culture assay are listed in Table 6. Agents that have demonstrated significant inhibitory effects on keratinocyte growth and differentiation in cell culture are listed in Table 7. Anti-infective agents were tested in cell culture using a colony forming efficiency (CFE) assay. Keratinocytes were cultured with irradiated 3T3 feeder cells in media containing the desired concentration of antibiotic. After 12 days, the cultures were stained and cell colonies were evaluated and scored. Controlled clinical trials on the effect of any of the anti-infectives on Epicel or prepared wound beds have not been conducted.

Table 6: Anti-infective Agents Tested on Epicel In Vitro No Significant Inhibitory Effects

Agent	**Maximum Dose[1]**
Amphotericin B	24 µg/mL
Bibiotic (Polymyxin B Sulfate & Bacitracin zinc)	200 U/mL, 50 /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 & 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

[1] 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.

Table 7: Anti-infective Agents Tested on Epicel In Vitro Significant Inhibitory Effects

Agent	Minimum Dose [1]
AK-Spore HC[2] (Polymyxin B sulfate, Neomycin sulfate, Hydrocortisone)	20 U/mL, 0.007 U/mL, 0.02 mg/mL
Acetic Acid	0.5%
Clotrimazole	0.1%
Miconazole	0.1%

[1] Minimum dose that inhibited keratinocyte growth and differentiation resulting in the number of growing colonies less than 50% of the control or the average growing colony size less than 50% of the control.

[2] The stated dilution of AK-Spore HC did show acceptable colony growth. However, since this concentration is too low to be of any clinical value, and all higher concentrations were unacceptable, the antibiotic was deemed unacceptable.

In addition to these in vitro data above, there is limited clinical experience with topical administration of the following agents in regard to potential effects on the cultured keratinocytes in Epicel: bacitracin zinc, fluconazole, imipenem, ketoconazole, and mupirocin.

Epicel may be applied in a single operation or in a series of operations, beginning approximately 17 days after cultures are initiated. The number of Epicel grafts required for each operation will be determined in advance based on the judgment of the treating physician, considering the patient's condition and the area of the wound to be covered.

Graft Application

Apply Epicel grafts topically to a prepared wound bed and attach Epicel securely in place with sutures or staples. During the grafting procedure, open the graft dishes only one at a time. Do not allow the grafts to dry before application to the wound bed.

1. Before treatment, obtain 3 to 5 aliquots (0.5 mL) of citrated or EDTA-anticoagulated plasma and ≥2 aliquots of viable, cryopreserved leukocytes (1×10^7 cells) blood samples for archival purposes. In the event that a xenogeneic infectious disease is suspected, baseline patient plasma and cells may be critical to determining etiology.
2. Once the wound bed is fully prepared, open the first graft dish. The Epicel graft will be lying in nutrient transport medium with the growing cells facing up.
3. Gently lift the graft by its backing using two forceps. A small silver orientation tag will be attached to the back of the graft.
4. Apply the graft to the wound bed with the growing cells against the wound and the supporting petrolatum gauze on the outside. The silver orientation tag should be facing up. Keep the handling of the graft to a minimum. Do not move the graft across the surface of the wound once it is applied.
5. Repeat the application procedure until all of the grafts are in place on the wound. Place the grafts as close together as possible without overlapping one another.

6. Once all of the grafts are applied, use a sufficient number of staples or sutures to firmly attach the grafts to the wound bed.
7. Apply a single layer of sterile nylon net over the supporting petrolatum gauze of the grafts. Staple the sterile nylon net in place and leave it undisturbed for 7 to 10 days or based on surgeon's assessment of the patient.
8. Apply four to five layers of absorbent gauze as a secondary outer dressing.

Postoperative Treatment

During the early postoperative period, avoid mechanical trauma and friction. Do not disrupt the underlying sterile nylon net or Epicel when changing the outer dressings. Avoid irrigation, particularly in the early stages after grafting due to the possibility of cell damage.

Change the outer absorbent dressing at least once daily to prevent accumulation of fluid and bacteria. Expose grafted areas to air at least four hours per day, preferably longer up to 12 hours as tolerated. Wounds having excessive discharge may require more frequent dressing changes and, if infected, may also require the use of topical antibiotics or other standard medical treatment. The outer absorbent dressings can be soaked in an antibiotic solution and then use the "wring-out" procedure prior to application to the graft area and changed approximately twice a day. Refer to the Pre-Grafting Considerations portion of the Instructions for Use section to choose an anti-infective agent that will not adversely affect the newly adherent grafts.

Seven to ten days after grafting, the sterile nylon net and petrolatum gauze can normally be teased away from the wound bed. The sterile nylon net and petrolatum gauze should be soaked in saline or sterile poloxamer-based, noncytotoxic wound cleanser to facilitate removal. If the petrolatum gauze is firmly adherent, the graft should be rewrapped with the gauze left in place. Attempt to remove the petrolatum gauze again in several days. Extreme care must be taken when removing the petrolatum gauze to prevent damage to the graft. If any portion of the grafted area is pulled away by removal of the petrolatum gauze, removal should be stopped.

After skin integrity has been established, medical judgment should be used in the choice of long-term care. Bathing with mild soaps and moisturizing with mild lotions are encouraged. Pressure garments are generally used beginning approximately six weeks post-grafting. Activity can be permitted as tolerated by the patient, recognizing that patients who have suffered extensive full-thickness burns or injuries may exhibit intolerance to heat and/or strenuous activity.

PATIENT COUNSELING INFORMATION

Each patient receiving Epicel® should be informed that murine (mouse) cells are used during the manufacture of Epicel. These cells have been extensively tested for the presence of infectious agents and shown to be negative; however, there exists a potential risk of exposure to unknown murine-derived infectious agents. Patients should be instructed to notify their physician of any symptoms of an allergic reaction. Patients should also be counseled to notify their treating physician of their prior treatment with Epicel if they develop skin cancers and/or unusual/unidentified infectious disease.

Epicel is considered to be a xenotransplantation product by the PHS and FDA. As such, Epicel recipients, but not their intimate contacts or health care providers, should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans.

A small amount of blood (around 20 mL) will be collected from patients before Epicel surgery. These blood samples will be further processed and stored indefinitely. The reason for collecting and storing this blood prior to skin grafting is to provide a baseline blood sample that may be needed in the future to assess any possible public health issues related to the treatment. Vericel will not use these blood samples for any purpose other than responding to a request by the regulatory agencies. The risks of having blood taken from a vein include bruising and bleeding. Additional risks include discomfort, pain, swelling, redness, and infection.

Also, all patients should be asked to consider allowing autopsy to be performed after death, regardless of the cause of death (even if it is a car accident, for example). A patient does not have to allow this, but it would let researchers investigate in the event of a public health concern. If a patient decides to allow this, it is important for the patient to share this information with their family and/or legal entity, since they will need to support this decision.

FDA requires manufacturers of certain medical devices to track those devices, and the patients who receive them, so they can notify the patients and their health care providers promptly if a safety concern associated with the device is identified. The FDA has determined that Epicel is a medical device that must be tracked. Vericel requests patient contact information of all Epicel recipients.

REFERENCES

1. Kowal-Vern A, Criswell BK. Burn scar neoplasms: literature review and statistical analysis. *Burns*. 2005. 31: 403-413.
2. Abdi MA, Yan M, Hanna TP. Systematic Review of Modern Case Series of Squamous Cell Cancer Arising in a Chronic Ulcer (Marjolin's Ulcer) of the Skin. JCO Glob Oncol. 2020 Jun;6:809-818. doi: 10.1200/GO.20.00094. PMID: 32530749; PMCID: PMC7328103.
3. Munster A. Cultured skin for massive burns: a prospective, controlled trial. *Ann. Surg*. 1996 September. 224: 372-377.

MANUFACTURED BY:

Vericel Corporation
64 Sidney Street
Cambridge, MA 02139 USA
1-800-232-7546 (USA only)
customercare@vcel.com

65009 Revision 11
November 2022