

Epicel[®]
cultured epidermal autografts (CEA)
HDE# 990002

Directions for Use

HUMANITARIAN DEVICE: Authorized by Federal law for use in patients who have deep dermal or full thickness burns comprising a total body surface area of 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.

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

DEVICE DESCRIPTION

Epicel[®] cultured epidermal autografts (CEA) 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 stainless steel surgical clips and measures approximately 50 cm² in area.

Epicel[®] is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (<http://www.fda.gov/cber/gdlns/xenophs0101.htm>) and the FDA Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (<http://www.fda.gov/cber/gdlns/clinxeno.htm>) as a xenotransplantation product because it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3, fibroblast feeder cells. 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 mycoplasmal 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 sterility via a pre-release sterility assessment and is verified for sterility by a standard 14 day sterility assessment, 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 and is 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 patients who have deep dermal or full thickness burns comprising a total body surface area of 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

Epicel[®] is contraindicated in patients with known hypersensitivity to agents used in the manufacture of Epicel[®] (please see the How Supplied section for a listing of manufacturing reagents).

Epicel[®] is cultured in media containing vancomycin and amikacin (and if clinically indicated from the patient's history, amphotericin is added). Trace quantities of these anti-infective agents may remain in the Epicel[®] autograft. Therefore, Epicel[®] should not be used in patients with a known history of anaphylaxis to these agents.

Epicel[®] should not be used in patients with known 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.

Epicel[®] is contraindicated for use on clinically infected wounds (see also Precautions).

WARNINGS

Although Epicel[®] is composed of autologous human cells from the patient, it is manufactured by co-cultivation with murine (mouse) cells and contains residual murine cells. Because Epicel[®] is co-cultivated with, and contains murine cells, FDA considers it a xenotransplantation product. Certain safety measures identified in the PHS Guideline on Infectious Disease Issues in Xenotransplantation regarding xenotransplantation recipients were recommended by the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) which met on January 13, 2000. The PHS and FDA recommend that xenotransplantation recipients and their intimate contacts should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans. However, the murine fibroblasts used in producing Epicel grafts were not considered by the subcommittee or FDA to

represent the same type of risk posed by many other xenotransplantation products. The murine cells have been extensively tested for viruses. Consistent with the discussion at the BRMAC Xenotransplantation Subcommittee, Epicel[®] recipients, but not their intimate contacts or healthcare providers should defer from donation. For more detailed information, the transcript of the BRMAC Xenotransplantation Subcommittee meeting may be accessed at the following FDA address:
<http://origin.www.fda.gov/cber/xap/trans.htm>.

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. Therefore, the Epicel[®] biopsy and the autologous Epicel[®] product may carry the risk of transmitting infectious diseases to health care providers handling these tissues. Accordingly, health care providers should employ universal precautions in handling the biopsy samples and the Epicel[®] product.

Discontinue use of 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.

PRECAUTIONS

Caution: Do not use Epicel[®] past its expiration date (24 hours).

Caution: Do not use Epicel[®] if package is opened or damaged.

Caution: Epicel[®] should be stored in its shipping container until ready for use.

Caution: Do not reuse, freeze, refrigerate, or sterilize after opening.

Caution: Do not allow the grafts to dry prior to application to the wound bed.

Caution: Do not refrigerate, freeze or incubate the Epicel[®] shipping container or its contents. The Epicel[®] product consists of viable, autologous cells packaged and labeled for use within specified time limits. The Epicel[®] transport container should remain closed and be kept at cool room temperature (13 to 23° C, 55 to 73° F). Epicel[®] should be kept out of the operating room until ready for application.

Caution: Do not use cytotoxic agents with Epicel[®]. Hibiclense[®] (chlorhexidine gluconate) should not be used to treat wound bed infections in patients who have received, or are expected to receive, Epicel[®]. Anti-infective 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 are listed in the Pre-grafting considerations section in the Directions for Use.

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

Caution: The recipient wound bed is believed to influence the success of keratinocyte graft application. Spontaneous blister formation may occur in patients grafted with keratinocytes alone and 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.

Caution: The anatomic site intended for graft application may also influence graft success. Mechanical stress has been implicated as one reason for graft blister formation.

Caution: Epicel[®] has been used since 1988. The long term safety of Epicel[®] is unknown. Preclinical information of the 3T3 cells and the final product, and clinical data collected to date, have not revealed a tumorigenic potential of the product. However, the long term potential of skin cancers arising from these cells is unknown.

Caution: 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 an infection can not be excluded. The risk of infection is unknown. It is also possible that symptoms of an infection may not be seen for months or years. To date, Genzyme Biosurgery is not aware of any infections related to murine cells.

Caution: 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 EVENTS

Since 1988, Epicel[®] has been used for the treatment of patients with third degree burn injuries. Genzyme Biosurgery has maintained an Epicel[®] database containing patient information supplied by attending burn teams. The database contains patient information collected from 1989 to 1996.

Table 1 summarizes the frequency of adverse events reported in $\geq 1\%$ of third degree burn patients who received treatment (n=552) with Epicel[®] from 1989 to 1996, without an assessment of causality.

Table 1
Adverse Events Reported in $\geq 1\%$ of Third Degree Burn Patients (n=552) Treated with Epicel[®] 1989-1996¹

Event	Number of Patients (%)	Number of Events
Death	74 (13)	74
Colonization/Infection	76 (14)	84
Graft shear ²	43 (8)	45
Blister	23(4)	25
Drainage	18(3)	18
Improper hemostasis	19(3)	19
Sepsis, septic shock	17(3)	17
Graft detachment ²	14(3)	14
Renal failure/disorder/dialysis	12(2)	12
Grafts debrided with dressing ³	11(2)	11
Slow wound healing	7(1)	8
Allergy ⁴	5(1)	5
Decreased vascular flow	5(1)	5
Improper takedown ³	6(1)	6
Amputation of extremity	4(1)	5
Contractures	3(1)	3
Fever	3(1)	3
Hypothermia	4(1)	4
Hematoma	3(1)	3
Multi-system failure	6(1)	6
Blood pressure (low, high)	4(1)	4

1. Attending burn teams reported Adverse Events in a non-standardized manner. Due to insufficient details, there is no knowledge of long-term sequelae.
2. A review of reports indicates that, in the majority of cases, "Graft Shear" and "Graft Detachment" were used to describe the partial or complete detachment of the graft due to mechanical trauma or friction during the procedure or early postoperative period.
3. A review of reports indicates that, in the majority of cases, "Grafts debrided with dressing" and "Improper takedown" described technical procedural errors in the care of the graft.
4. A review of reports indicates that "Allergy" was an event experienced due to an agent other than the Epicel[®] graft.

One lower extremity amputation not included in the database occurred in an epidermolysis bullosa dystrophica (DEB) patient treated with Epicel[®] that developed an invasive squamous cell carcinoma (SCC). A specimen of the patient's graft did not cause tumor formation in nude mice. SCC is a known complication of DEB. Although the role of Epicel[®] in the causation of SCC can not be excluded, there is no information to suggest that such a causal relationship exists.

A review of the adverse event data received by Genzyme and reported to FDA from June 1998 through August 2006 revealed that the events were similar to the previously identified adverse events. **Table 2** summarizes the frequency of adverse events that

occurred in $\geq 1\%$ of third degree burn patients (n=734) who received treatment with Epicel[®] during the period reviewed. The relationship of these events to Epicel[®] has not been established.

Table 2
Adverse Events Reported and Occurring in $\geq 1\%$ of Third Degree Patients (n= 734) Treated with Epicel[®] from June 24, 1998 through August 31, 2006

Event	Number of Patients (%)	Number of Events
Death ¹	65 (9%)	65
Sepsis	27 (3.7%)	27
Multi-organ failure	24 (3.3%)	24
Skin graft failure/Graft complication	10 (1.3%)	10

1. In accordance with standard coding conventions, after August 2000, death was collected as an outcome and was not coded as an event term unless no other term was provided. Combining the n for the adverse event coded term death [n=30] and the n for death as an outcome only [n=35], the death total is n=65 (9%).

CLINICAL INFORMATION

Clinical data of burn patients treated with Epicel[®] is presented from two sources:

1. Genzyme Biosurgery Epicel[®] Clinical Experience (database).
2. Munster Study: a physician-sponsored evaluation conducted by Dr. Andrew Munster at Johns Hopkins Burn Center, Baltimore, Maryland (Ann Surg. 1996; 224(3):372-5).

Clinical Data

1. A. Genzyme Biosurgery Epicel[®] Clinical Experience (database, 1989 to 1996)

Since 1988, Genzyme Biosurgery has supplied Epicel[®] for the treatment of approximately 1300 patients with burn injuries. The product had been considered a banked human tissue until 1996 when FDA announced that manipulated autologous cell-based products used for structural repair or reconstruction (MAS cell products, <http://www.fda.gov/cber/gdlns>) required regulatory oversight. Genzyme Biosurgery has collected information from 1989 to 1996 on patients receiving Epicel[®] and has entered the information into a database, relying on information supplied by the attending burn team.

For this time period, Genzyme's database contains data for 552 patients. Demographic, clinical outcome (survival), and adverse event data were recorded for patients who were treated with Epicel[®] (mean number of grafts = 104, range of 4-408). These patients show a survival rate of 86.6% (478/552) at 3 months, post initial

surgery. A summary of this data is shown in **Table 3** (refer to Table 1 for adverse events reported for these patients).

Table 3
Epicel® Database:
Patient Demographics and Characteristics

	Total Treated Patients n	Survived n (%)
Number of Patients	552	478 (86.6)
Sex		
Male n (%)	409 (74.1)	355 (74.3)
Female n (%)	116 (21.0)	98 (20.5)
No Data n (%)	27 (4.9)	25 (5.2)
Mean 3rd Degree Burn¹ (%)	56.1 ± 21.2	54.4 ± 20.9
Mean Age (yrs)	28.7 ± 18.1	27.9 ± 17.4
Mean TBSA² (%)	68.6 ± 17.4	67.6 ± 17.1
Inhalation Injury³ n (%)	195 (35.3)	159 (33.3)

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.

B. Clinical Information: 1997 to 2006

Data collected on patients treated with Epicel® from 1998 to 2006 was limited in scope, e.g., serious adverse events (see Table 2, AEs from 1998-2006), TBSA, number of grafts used and mortality. During 1997, only survival data was collected (55 patients treated, 7 deaths (13%)). The incidence of adverse events observed from 1998-2006 appears similar, if not lower, than the incidence of adverse events observed in the 552 patients treated from 1989 to 1996.

2. Munster Study (Munster, 1996)

This published article reported on an independent, physician-sponsored study that compared the outcome of therapy in patients with massive burns with or without cultured epidermal autografts. 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 cultured epithelial autograft (CEA), i.e., Epicel®. All patients for entry into the study had to

satisfy the following criteria: 1. a minimum burn size of 50% with a substantial third-degree component, and 2. survival beyond the first operative procedure for excision and initial coverage. Genzyme Biosurgery was able to collect data from the medical records of 44 of the patients in this study. A summary of this data is shown in **Table 4**.

Table 4
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)
Death n (%)	2 (10.0)	15 (62.5)

HOW SUPPLIED

Each Epicel® graft consists of a sheet of cultured epidermal cells attached with stainless steel 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 approximately 50 cm². 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 Eagles Medium (DMEM) and shipped within secondary packaging capable of maintaining the appropriate storage temperature for up to 24 hours. 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: Epicel[®] is to be stored in the original shipping container in which it is received. Maintain the shipping carton at cool room temperature (13 to 23° C, 55 to 73° F). Do not store in a refrigerator or freezer. Do not remove from original shipping container until ready for use.

Package inspection: Visually inspect the Epicel[®] packaging and insure that it is intact. If the packaging is damaged, the product is not acceptable for patient application. Visually inspect the medium in which Epicel[®] is transported. The medium should not appear cloudy. Any cloudiness of the medium is an indicator that the device is not acceptable for patient application.

DIRECTIONS FOR USE

Pre-grafting considerations

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.

Epicel[®] is more sensitive to wound bed conditions and colonization than 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 5**. Agents that have demonstrated significant inhibitory effects on keratinocyte growth and differentiation in cell culture are listed in **Table 6**. 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 5
Anti-infective Agents Tested on Epicel[®] *In Vitro*
No Significant Inhibitory Effects

Agent	Maximum Dose ¹
Amphotericin B	24 µg/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
Bibiotic (Polymyxin B Sulfate & Bacitracin zinc)	200 U/mL, 50 U/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 6
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%
Clostrimazole	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, there is a limited degree of clinical experience with topical administration of the following agents: Bacitracin Zinc, Clavulanate Potassium, Fluconazole, Imipenem, Kanamycin Sulfate, Ketoconazole, Mupirocin, Ticarcillin disodium.

Epicel® may be applied in a single operation or in a series of operations, beginning approximately 15 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

Epicel® grafts are applied topically to a prepared wound bed and attached securely in place with sutures or staples. During the grafting procedure, the graft dishes should be opened 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.
2. Gently lift the graft by its backing using two forceps. A small silver orientation tag will be attached to the back of the graft.

3. 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. Handling of the graft should be kept to a minimum and the graft should not be moved across the surface of the wound once it is applied.
4. Repeat the application procedure until all of the grafts are in place on the wound. The grafts should be placed as close together as possible without overlapping one another.
5. Once all of the grafts are applied, a sufficient number of staples or sutures should be used to firmly attach the grafts to the wound bed.
6. Apply a single layer of sterile coarse mesh gauze over the supporting petrolatum gauze of the grafts. The gauze should be stapled in place and left undisturbed for 7 - 10 days.
7. Apply four to five layers of absorbent gauze as a secondary outer dressing.

Postoperative Treatment

During the early postoperative period, mechanical trauma and friction should be avoided. Do not disrupt the underlying sterile coarse mesh gauze or Epicel[®] when changing the outer dressings. Avoid frequent irrigation, particularly in the early stages after grafting due to the possibility of cell damage.

The outer absorbent dressing should be changed at least once daily to prevent accumulation of fluid and bacteria. 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 prior to application to the graft area and changed approximately twice a day. Refer to the Pre-grafting considerations portion of the Directions 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 coarse mesh and petrolatum gauze can normally be teased away from the wound bed. The coarse mesh and petrolatum gauze should be soaked in saline or Shurclens[®] 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 is 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 that if they develop skin cancers or unusual or unidentified infectious disease to notify their treating physician of their prior treatment with Epicel[®].

Although Epicel[®] is composed of autologous human cells from the patient, it is manufactured by co-cultivation with murine (mouse) cells and contains residual murine cells. Because Epicel[®] is co-cultivated with, and contains murine cells FDA considers it a xenotransplantation product. Certain safety measures identified in the PHS Guideline on Infectious Disease Issues in Xenotransplantation regarding xenotransplantation recipients were recommended by the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) which met on January 13, 2000. The PHS and FDA recommend that xenotransplantation recipients and their intimate contacts should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans. However, the murine fibroblasts used in producing Epicel grafts were not considered by the subcommittee or FDA to represent the same type of risk posed by many other xenotransplantation products. The murine cells have been extensively tested for viruses. Consistent with the discussion at the BRMAC Xenotransplantation Subcommittee, Epicel[®] recipients, but not their intimate contacts or healthcare providers should defer from donation. For more detailed information, the transcript of the BRMAC Xenotransplantation Subcommittee meeting may be accessed at the following FDA address: <http://origin.www.fda.gov/cber/xap/trans.htm>.

FDA, together with other PHS agencies, is developing a computerized National Xenotransplantation Database (NXD) intended to assist in the monitoring and tracking of xenotransplantation recipients for Public Health Service needs. Physicians and patients using the Epicel[®] product should be aware that once the Database becomes operational, Genzyme will supply the information requested to the appropriate agency. Subject identification will be encoded to protect patient privacy. To the extent allowed by law, information derived from the NXD may be available to the public with appropriate confidentiality protections of possible proprietary or individually identifiable information. In addition, a small amount of blood (around 30 mL, which is equivalent to about 6 teaspoons) will be collected from patients before Epicel[®] surgery. These blood samples will be further processed and stored indefinitely. Genzyme Biosurgery 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.

To date there has been no identified public health hazard associated with the use of xenogeneic cells in the Epicel[®] manufacturing process. The purpose of collecting information for the NXD and baseline blood samples from Epicel[®] recipients is for possible use to facilitate public health investigations should any possible public health issues related to the treatment arise in the future.

PEEL-OFF LABEL

The peel-off label provided with the Epicel[®] product should be applied to the patient's medical record to document that the patient has been treated with Epicel[®] that is manufactured using murine cells.

MANUFACTURED BY:

Genzyme Biosurgery,
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617-494-8484 or 1-800-232-7546 (USA only)
Epicel[®] is a Registered Trademark of Genzyme Corporation in the U. S.