

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

Patient Information

The following information is intended for burn patients and their families to learn about Epicel (cultured epidermal autografts). We provide this information so that patients and their families can be educated on the treatment that a burn patient may receive.

Epicel is a 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.

Federal Law restricts this device to sale by or on order of a physician.

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Glossary/Definitions of Terms

Anaphylaxis: immediate, transient kind of allergic reaction.

Autograft: a tissue transferred from one place on the body to a new location.

Autologous: when a tissue is moved from one place on the body to another location on the same body, the tissue is referred to as autologous.

Cultured: the maintenance or growth of cells in an incubator after removal from the body.

Cultured Epidermal Autograft: a tissue grown from one's own skin cells for use in placing on the person's own body.

Epidermis: the outer cell layers of the skin.

Epidermal: relating to the outer cell layers of the skin.

Dermal: relating to the skin.

Dermis: skin, the layer of skin lying under the epidermis, it contains blood vessels, nerves, sweat glands, and hair follicles.

Full thickness burn: a burn of the skin that involves all of the layers of skin, i.e., epidermis and dermis, down to the underlying muscle and fat tissues. A full thickness skin burn is a third degree burn.

Harvest: word used to indicate removal of skin tissue for use in covering burns on other parts of the body.

Hypersensitivity: condition in which there is an exaggerated response by the body to a foreign agent.

Irradiated or Irradiation: the use of or process of using gamma-ray energy to inactivate cells used in the manufacture of Epicel; cells treated with this process can not reproduce but remain alive.

Media or Medium: liquid or solid reagents used for the growth of cells outside of the body.

Mouse cells (3T3 cells): cells from mice used to help the patient's keratinocytes/skin cells grow.

Regeneration: growth of skin cells to replace the patient's own skin lost to burn.

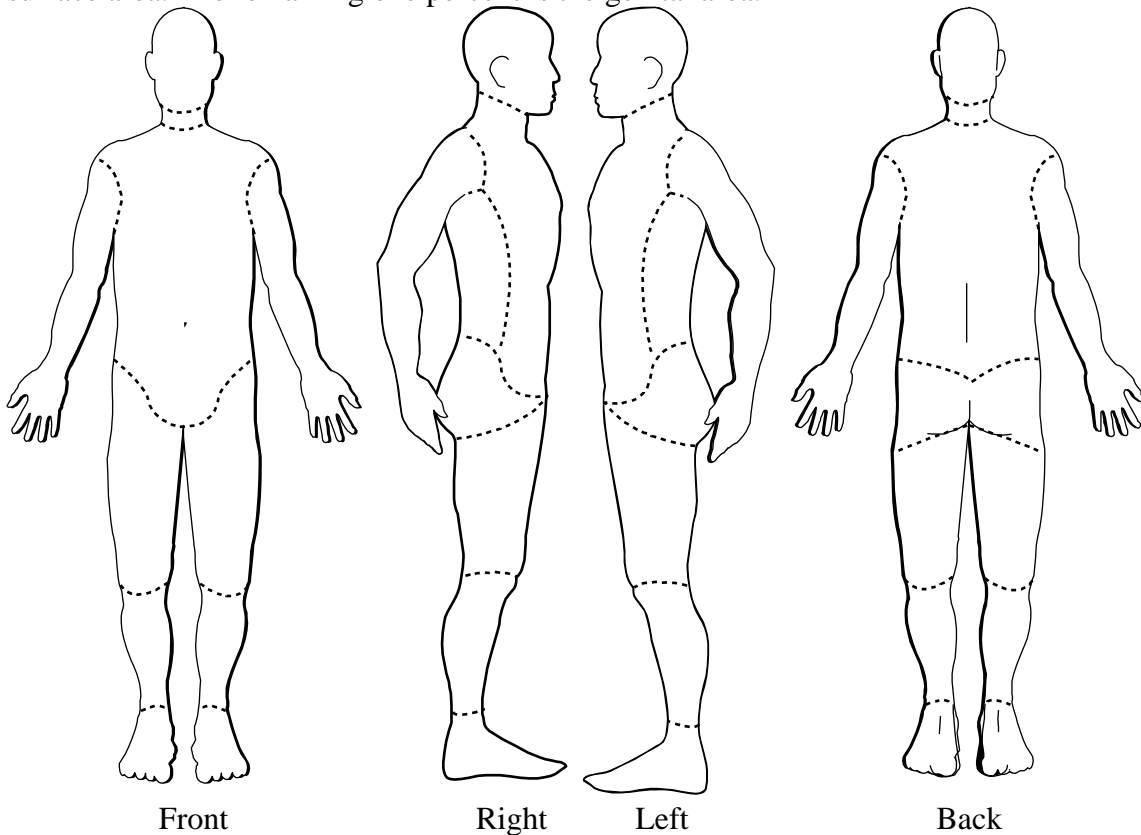
Skin grafts: skin used for replacing skin lost to burn; also can refer to skin cells grown outside of the body to replace skin lost to burn.

Split-thickness autograft: process of removing part of patient's own skin for immediate placement onto burned areas of the patient's own body.

Tissue: a collection of similar cells grown or growing together.

Tissue culture: the process of growing cells outside of the body in an incubator.

Total Body Surface Area (TBSA): a percent estimate of the total surface of the body that is burned. Burns are judged by the size of the burn in relation to the whole body and by the depth of the burn injury. Different methods exist to calculate the extent or size of a burn injury. It is important to know the percentage of the total skin surface involved in the burn. One method to determine the percentage of total skin surface involved in a burn is to divide the adult body into regions. Each region represents approximately nine percent of the total body surface. These regions are the head and neck, each upper limb, the chest, the abdomen, the upper back, the lower back and buttocks, the front of each lower limb, and the back of each lower limb. This makes up 99 percent of the total body surface area. The remaining one percent is the genital area.



Xenogenic: referring to being derived or obtained from an organism of a different species, e.g., tissue grafts.

Xenotransplantation: used to refer to tissues being placed from one species to another species, e.g., from mouse to human; the process of placing tissues from one species onto another species.

Indications for Use

Epicel is indicated for use in patients who have deep dermal or full thickness burns over a total body surface area of greater than or equal to 30%. It may be used 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.

Your Condition and Why Epicel May Help

In full thickness burns, the outermost layer (epidermis) of the skin and all of the dermis (inner layer of the skin) is destroyed. Due to the depth of the injury, regeneration of the skin is greatly reduced. The usual treatment for these deep wounds is removal of the damaged tissue and placement of a fresh skin graft. These skin grafts are taken from an area of the individual's unburned skin. This donor skin is placed on the burn wounds. Wound healing may occur fairly rapidly in patients with small total body surface area burns where there is enough unburned skin to harvest for a graft. In a larger total body surface area (usually greater than 30%) the patient does not have enough donor skin available to cover the wounds. The physician may need to consider another means of permanent wound closure, such as Epicel. You have been burned to the extent and degree that your physician believes Epicel may be useful in helping your wounds heal. Epicel is made from your own cells after they have grown for a period of time in an incubator. The Epicel graft replaces the epidermal or top layer of the skin. This layer of skin is required to close or heal your wounds. This permanent wound coverage must be performed in a timely fashion to avoid the many complications of the burn wound injury.

Device Description

Epicel grafts are sheets of skin cells ranging from 2 to 8 cell layers thick. The grafts are grown or cultured from a postage stamp sized sample of patient's own healthy skin, which is sent to Genzyme Biosurgery for processing. The cells within the epidermis of the skin sample are separated and grown by a process called "tissue culture", which involves feeding the cells with specific nutrients and maintaining strict climate controls so that the cells multiply to form sheets of skin. During this process, irradiated mouse cells, also referred to as 3T3 cells, are used to promote cell growth and to ensure that there will be a sufficient number of grafts available as soon as possible for treatment.

The mouse cells used in the culture process have been extensively tested for the presence of infectious agents. Those tests include sterility testing for bacteria, fungi, and viruses. The mouse cells are irradiated before their use in the process to prevent them from multiplying.

Other substances used during the manufacture of Epicel include: antibiotics such as vancomycin, amikacin or amphotericin B; bovine (cow) serum; hormones such as insulin, triiodothyronine, hydrocortisone, epidermal growth factor; and also cholera enterotoxin.

When Epicel Should Not be Used

Epicel should not be used in patients with known hypersensitivity or allergy to substances used in the manufacture of Epicel.

Epicel should not be used in patients who have a known history of anaphylaxis or allergic reactions to antibiotics, vancomycin, amikacin or amphotericin because Epicel is cultured in media containing vancomycin and amikacin (and for certain patients, amphotericin is added). Trace quantities of these antibiotics may remain in the Epicel autograft.

Epicel should not be used in patients who have sensitivities to materials of cow or mouse origin. The cell culture medium used in the production of Epicel contains cow serum and the cells are cultured together with mouse cells. The medium used to package and transport Epicel does not contain cow serum; however, trace quantities of cow-derived proteins may still be present.

Epicel[®] should not be used on infected wounds.

Xenotransplantation and Tissue Donation Issues

Although Epicel is composed of autologous human cells from your skin; it is grown together with mouse cells and contains residual mouse cells. Because Epicel contains mouse cells; FDA considers it a xenotransplantation product. Certain safety measures identified by the Public Health Service (PHS) and FDA are recommended for Epicel recipients:

Never donate blood or blood parts, tissue, breast milk, egg, sperm, or other body parts for use in humans because of the potential risk of carrying an infection that is transmitted from mouse cells to humans.

Although the mouse cells used in the Epicel manufacture 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. However, Epicel has been manufactured and used on patients since 1987 and to date Genzyme Biosurgery is not aware of any infections related to mouse cells. Patients should notify their physician immediately of any symptoms of an infection or allergic reaction.

The need to defer from tissue donation does not extend to intimate contacts and healthcare providers of Epicel recipients. FDA, along with other PHS agencies, is developing a computerized National Xenotransplantation Database (NXD) to assist in the monitoring and tracking of xenotransplantation recipients. 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 coded to protect patient privacy. To the extent allowed by law, information derived from the NXD may be available to the public.

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. 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. The PHS, FDA or other regulatory agency may use these blood samples in the investigation of a public health concern. 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 will 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 in public health investigations if public health issues related to the treatment arise in the future.

Potential Complications of Burns and Skin Grafting in General

Extensive burns that involve the full thickness of the skin and cover large areas of the body can cause many complications to both the skin and other parts of the body. These complications can be very serious and life threatening. They can include local or general infection, lung, kidney, and circulation problems. Treatment for burns of this nature includes skin grafting and treatment for the other general organ system problems associated with extensive burns.

Infection is the most commonly reported complication identified in burn patients treated with skin grafts (e.g., Epicel, split-thickness autografts, and/or artificial skin substitutes). Other problems associated with skin grafting include: blister formation, graft tearing, and graft detachment. Graft contracture, or skin tightening, can occur in individuals who have been skin grafted for their burns.

Clinical Experience with Epicel

Since 1988, Genzyme Biosurgery has supplied Epicel for the treatment of approximately 1300 patients with burn injuries. Genzyme has an Epicel database containing patient information supplied by the attending burn teams as the source for patient data. The database contains information from 552 patients collected from 1989 to 1996.

Demographic, clinical outcome, and adverse event data were recorded for patients who were treated with Epicel. These patients show a survival rate of 86.6% (478/552) at 3 months, post initial surgery. The adverse events of highest incidence by patient were: death (13%), infection (14%), and graft tear (8%) or graft blister (4%). Some of these events may have been due to the underlying burn injury and not the device itself.

In addition, Genzyme maintains a separate database for all adverse events reported to the company. From June 1998 through August 2006, 734 patients were treated with Epicel. During this period, no new types of adverse events were reported. Events that were reported in $\geq 1\%$ of patients included death (9%), sepsis (3.7%), multi-organ failure (3.3%) and skin graft failure/graft complication (1.3%). The relationship of these events to Epicel has not been established.

The information indicates that Epicel is a potential treatment option in the care of patients with severe, life threatening burns. Adverse events reported with the use of Epicel are typical of those seen with burn injuries. It is well understood that permanent wound closure must be achieved in a timely fashion to avoid the many complications of the burn injury. The information demonstrates that Epicel may be useful in addition to traditional wound closure with split thickness skin grafts, particularly in the treatment of those severely burned patients who do not have sufficient skin to graft the entire burn.

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.

Long-Term Care - After Skin Integrity Has Been Established

After skin integrity has been established, your doctor will decide on the best long term care for you. 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. Patients who have suffered extensive full-thickness burns or injuries may exhibit intolerance to heat and/or strenuous activity.

Additional Information and Questions

Please refer to the Epicel package insert for additional information. This can be obtained from your physician or by contacting Genzyme Biosurgery 24 hours/day @ 800-CEA-SKIN or 1-800-232-7546 (USA only) or from Genzyme web site- www.genzyme.com.

For any concerns regarding treatment with Epicel please contact your physician.

For any product-related questions, please contact
Genzyme Biosurgery 24 hours/day @ 800-CEA-SKIN or 1-800-232-7546 (USA only).