Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy, OBPV, CBER
Through:	Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Annual Safety Update for the Pediatric Advisory Committee (PAC)
Sponsor:	Vericel
Product:	Epicel (cultured epidermal autografts)
STN:	HDE# BH 990200/92
Indication:	Epicel is indicated for use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area (TBSA) 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.

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this is an annual safety update for the Pediatric Advisory Committee (PAC), based on the postmarket experience with the use of a humanitarian use device, Epicel (cultured epidermal autografts), manufactured by Vericel. This review provides updated postmarket safety data, so the Committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This memorandum documents FDA's complete evaluation, including review of postmarket medical device reporting (MDR) of adverse events, annual reports from the manufacturer, and the peer-reviewed literature associated with the device.

II. 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 (TBSA) 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.

III. DEVICE DESCRIPTION

Epicel 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 approximately 50 cm^2 in area.

Epicel is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation and FDA[1] as a xenotransplantation product, because it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3 fibroblast feeder cells.

Depending on the surface area requiring coverage, more than one graft may be used per patient. For example, 90.1 was the average number of Epicel grafts used per patient during the period from 2008 through 2014 (Review Memo BH990200/34, February 18, 2016). From 1989 to 1996, each patient received an average of 104 grafts (Epicel Directions for Use [February 2016], Clinical Studies section).

[1] Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans

IV. REGULATORY HISTORY

- 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated product.
- 1998: FDA designated Epicel as a combination product and as a Humanitarian Use Device (HUD).
- 2007: FDA's Center for Devices and Radiologic Health (CDRH) approved Epicel under the HDE regulatory statute.
- 2013: Lead regulatory responsibility for the Epicel HDE was transferred to the Center for Biologics Evaluation and Research (CBER) based on an assessment of the primary mode of action under the Combination Products regulations. This change was part of a transfer of oversight responsibilities for certain wound care products containing live cells from CDRH to CBER.
- 2014: FDA approved a labeling supplement to revise Directions for Use and Patient Information to describe the risk of squamous cell carcinoma (SCC).
- 2014: Epicel ownership was transferred from Genzyme to Vericel.
- 2016: FDA approved a pediatric labeling supplement, which specified use in both adult and pediatric patients, added pediatric labeling information, and granted an exemption from the profit prohibition.
- 2017: First Annual Review of Pediatric Safety for Epicel was presented to PAC in March 2017. (This has been followed by subsequent annual safety updates for the PAC.)

V. PEDIATRIC USE

In 2007, Epicel received marketing approval under Humanitarian Device Exemption (HDE) regulations, for use in patients who have deep dermal or full thickness burns in ≥30% of body surface area. Since marketing approval in 2007 to 2015, approximately 29% of patients treated with Epicel worldwide were pediatric patients (age < 22 years). In 2016, FDA approved a pediatric labeling supplement, which specified use in both adult and pediatric patients, added pediatric labeling information, and granted an exemption from the profit prohibition. The Directions for Use (DFU) summarizes adverse reaction report information for 205 pediatric patients treated with Epicel from 1989 to 1996, and an additional 589 pediatric patients treated from 1998 to 2015. These were also summarized in the pediatric safety memo dated March 7, 2017 for PAC review.

VI. ANNUAL DISTRIBUTION NUMBER/ANNUAL SALES NUMBERS

Section 520(m)(6)(A)(ii) of the FD&C allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN).

The currently approved ADN for Epicel is 360,400 grafts. The ADN was calculated as 90.1 x 4000 = 360,400 Epicel grafts; where 90.1 was the average number of Epicel grafts used per patient from 2008 through 2014 (Review Memo BH990200/34, ADN calculation, Feb. 18, 2016); 4000 individuals represents the target population per the HDE definition at the time the pediatric labeling was approved (February 2016).

The number of Epicel grafts distributed has not exceeded the ADN. The number of Epicel grafts distributed during:

- Calendar year 2021: (b) (4) Epicel grafts, including 2,565 grafts in pediatric patients.
- Calendar year 2022: Not yet available, however, from January 1, 2022 through September 30, 2022, Vericel distributed (b) (4) Epicel grafts, including 1,672 grafts in pediatric patients.

Note: These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

During the annual review period, October 1, 2021 to September 30, 2022, 20 pediatric patients, (b) (4) adult patients, and (b) (4) patients of unknown age were treated with Epicel for burn injuries.

VII. LABEL CHANGES IN REVIEW PERIOD

There were no label changes during the PAC review period (October 1, 2021 to September 30, 2022). On November 18, 2022, FDA approved a labeling supplement (BH990200/89) to update the Warning section under Squamous Cell Carcinoma (SCC) of the Instructions for Use (IFU) following an updated sponsor assessment, based largely on a literature review. Revisions were made to the Warning for SCC and Patient Information Pamphlet to update the time to onset (latency period) for SCC following Epicel grafting. (Please see section XI of memorandum for discussion of SCC cases.)

VIII. MEDICAL DEVICE REPORTS (MDRs)

A. Strengths and Limitations of MDR Data

The FDA receives MDRs of suspected device-associated deaths, serious injuries, and malfunctions from mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of

these products.

MDR reports can be used to:

- Establish a qualitative snapshot of adverse events for a device or device type
- Detect actual or potential device problems including:
    - rare or unexpected adverse events;
    - adverse events that occur during long-term use;
    - adverse events associated with vulnerable populations;
    - off-label use; and use error.

Although MDRs are a valuable source of information, this Medical Device Reporting is a passive surveillance system and has limitations, including the submission of incomplete, inaccurate, untimely, unverified and/or additionally biased data. In addition, the incidence of an event cannot be determined from MDRs alone due to under-reporting of events and lack of information about frequency of device use.

Limitations of MDRs include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused an event can be difficult based solely on information provided in MDRs. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias due to, reporting practices, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

B. MDRs Associated with EPICEL

The MDR database was searched on November 2, 2022, to identify postmarket adverse event reports associated with the use of Epicel submitted to FDA during the annual review period, October 1, 2021 to September 30, 2022. The search identified 8 MDRs, including 2 reports with fatal outcomes, 1 report with serious injury, and 5 reports of device malfunction. No report involved a pediatric patient. All 8 reports were submitted by the manufacturer. The two patients with fatal outcomes sustained burn injury but the extent of burn injury was not reported in these two cases. As per the manufacturer's assessment, these deaths were unrelated to the use of Epicel. The summary of death and injury reports is displayed in Table 1.

Table 1. Summary of Death and Injury Reports (n=3)

Case ID	Age (year)	Sex	Event	Time from Graft to Event	Cause of Death/PT
(b) (6)	42	Male	Serious injury	7 days	Seizure, cyanosis, stopped breathing, hypotension
	unknown	unknown	Death	25 days	Multi-organ failure
	40	Male	Death	13 days	Cardiac failure

Reviewer comment: The reported causes of deaths are consistent with complications experienced by severe burn trauma patients in the intensive care setting. No new safety concerns were identified.

The five reports of device malfunction involved media leakage in the graft bags. Table 2 provides a summary of 5 device malfunction reports.

Table 2. Summary of Device Malfunction Reports (n=5)

Case ID	Event	Lot	Description of event
(b) (6)	Malfunction	EE02643E	Media leak in one of the plastic sleeves
	Malfunction	EE02715	Fluid in a sleeve containing the grafts
	Malfunction	EE02920A	Media in the bottom outer graft package
	Malfunction	EE02929	A leak in the middle pouch
	Malfunction	EE02917B	Media leak in one of the plastic pouches

*Reported in previous period

Reviewer comment: Two of these five cases were updates on cases that were initially reported in the previous reporting period. In response to an information request, the sponsor provided additional information on malfunction reports related to media leakage. The sponsor stated:

> *"There were three unique cases in this reporting period where media was found in the self-seal pouch in which the graft dishes are contained. All three cases were reported before process improvement steps were fully implemented to the*

Method ((b) (4)) and Manpower (training) as previously communicated to the Agency (Correspondence dated 01Nov21). The process improvement steps included retraining's and improvements to preventative maintenance, (b) (4) parameters, and engineering studies to evaluate the (b) (4) ."

It is important to note that the above malfunction reports related to media leakage, were not associated with clinical adverse events. Additionally, not all grafts were implanted. Please see additional discussion in section IX (Table 4 includes all product issues in the annual reporting interval, including the above 5 malfunctions reported to the MDR database). The total number of product issues related to media leakage has decreased in this annual reporting period (3 new reports) compared to the previous annual reporting period (7 reports). FDA will continue routine surveillance for device malfunction reports.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (September 1, 2021, to August 31, 2022) was reviewed. During the reporting period, a total of 34 events (24 serious events, 10 nonserious events) were reported in 34 patients. There was a decrease in the number of events received during this reporting period compared to the previous reporting period (34 events vs 38 events). The sponsor stated: "This may be due to the fewer number of patients treated during this reporting period compared to the previous reporting period ((b) (4) patients vs (b) (4) patients)."

The most frequently reported system organ class (SOC) category during this reporting period was Product Issues (41.2%;14/34); General Disorders and Administration Site Conditions (20.6%; 7/34); Neoplasms benign, malignant, and unspecified (including cysts and polyps) (14.7%, 5/34); Infections and infestations (5.9%, 2/34); Respiratory, thoracic, and mediastinal disorders (5.9%, 2/34); and Vascular disorders (5.9%, 2/34). Of the 34 reports, 9 reports involved fatal outcomes, of which there were 6 adult reports and 3 reports that occurred in patients of unknown age.

Pediatric Death Reports: There were no reports with fatal outcome in pediatric Epicel recipients.

Adult Death Reports: The sponsor received 9 reports involving fatal outcomes in adult Epicel recipients or Epicel recipients of unknown age during the reporting period of the Annual Report. These 9 cases, including 2 cases identified in the MDR database (described in section VIII.B), are displayed in Table 3.

Table 3: Summary of Case Reports with Fatal Outcome Received during the Reporting Period – All Age Groups

Case ID	Age Sex	Event	Time from Graft to Event	Cause of Death
(b) (6)	29 years Female	Death	90 days	Thermal burn
	Unknown	Death	28 days	Unknown
	Unknown	Multiple organ dysfunction syndrome	25 days	Multiple organ dysfunction syndrome
	40 years Male	Cardiac failure	13 days	Cardiac failure
	64 years Male	Death	47 days	Unknown
	75 years Male	Death	Unknown	Unknown
	42 years Male	Sepsis	-33 days	Sepsis
	Unknown Male	Infection	Unknown	Infection
	33 years Male	Squamous cell carcinoma	16 years	Squamous cell carcinoma

*Case reported to MDR database

[a] One case of SCC reported in the literature (Baus 2021) had a fatal outcome.

Reviewer comment: Most reports of death following Epicel were related to multiple organ dysfunction, cardiac events, or sepsis, representing known complications with underlying burn injuries. Squamous cell carcinoma is a known risk for Epicel and the label includes a Warning to further describe SCC reports following Epicel.

Squamous Cell Carcinoma (SCC)

The sponsor's Annual Report included eight cases of SCC in adult patients, seven of which were identified in literature articles from a literature review conducted in 2022, and one of which was a spontaneous case report ((b) (6) , not submitted to MDR) (details in Section XI). As noted previously (see section VII), the sponsor's updated review of SCC reports led to a safety-related label change that was approved on November 18, 2022.

Product Issue Reports: Sixteen (16) product issue reports, including 5 device malfunction reports submitted to the MDR database (previously described in section VIII), are summarized in the table 4 below.

Table 4. Summary of Product Issue Reports (n=16)

Case ID	Event	# Grafts Utilized	# Grafts Not Utilized	Lot No	Description of event	Outcome
(b) (6)	Device Malfunction	99	0	EE02643E	Media Leak	No adverse event
	Device Malfunction	55	16	EE02715	Media Leak	No adverse event
	Device Malfunction	61	11	EE02920A	Media Leak	No adverse event
	Device Malfunction	53	7	EE02929	Media Leak	No adverse event
	Device Malfunction	42	16	EE02917B	Media Leak	No adverse event
	Physical property	45	27	EE02847	Graft shearing	No adverse event
	Physical property	52	20	EE02848	Graft shearing	No adverse event
	Physical property	34	38	EE02857	Graft shearing	No adverse event
	Physical property	54	42	EE02854A	Graft shearing	No adverse event
	Physical property	66	33	EE02848A	Graft shearing	No adverse event
	Physical property	27	10	EE02867	Graft shearing	No adverse event
	Physical property	5	10	EE02938	Graft shearing	No adverse event
	Physical property	60	7	EE02957	Graft shearing	No adverse event
	Physical property	79	24	EE02989	Graft shearing	No adverse event
	Physical property	130	14	EE02997	Graft shearing	No adverse event
	Physical property	39	5	EE02997A	Graft shearing	No adverse event

*Case reported to MDR database

Five of the 16 product issue reports were related to media leaks that were previously

discussed in section VIII. In the remaining reports, one or more grafts were identified as being unusable due to shearing. As per the sponsor, none of the sheared grafts were used (Table 4 provides breakdown of grafts and shows that not all grafts were utilized). In response to an information request, the sponsor stated: “there are three potential root causes to graft shearing: (b) (4) ” In response to these findings, the sponsor conducted the following retrainings: (b) (4) The sheared grafts were not used on patients, and no adverse events were reported for these patients.

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 2, 2022, using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts” OR "cultured epithelial autograft" OR "cultured epidermal autograft” for articles published between October 1, 2021 and September 30, 2022, retrieved 11 articles. Titles and abstracts were reviewed for relevance to safety information specifically for Epicel device and its labeled indication. One article relevant to Epicel AEs was identified and is summarized in the table below. This article was included in the Sponsor’s Annual Report in section IX.

Article	Clinical Summary
Baus A, et. al. Marjolin ulcers after cultured epidermal autograft in severely burned patients: a rare case series and literature review. [Article in French] Eur J Dermatol. 2021 Dec 1;31(6):759-770.	A retrospective review conducted at a single institution (Military hospital of Clamart) in France included 34 patients treated for burns with CEA between 1991 and 2013. Four cases of SCC occurred in area previously covered by CEA. The average time to malignant transformation was 15.7 years (range: 14-19 years)

XI. ADVERSE EVENT OF SPECIAL INTEREST: Squamous Cell Carcinoma (SCC)

SCC is the most common skin cancer to develop from burn wound scars. The label (please see Appendix B) for Epicel includes information on the risk of SCC[2] (Instructions for Use [IFU] –Warnings section, and Patient Information). As stated in the label, "Although SCC is a known complication of burn scars and DEB, the role of Epicel in the causation of SCC cannot be excluded."

Five cases of SCC observed in Epicel-treated burn patients were reviewed and discussed during the initial PAC presentation on March 7, 2017. No new cases of SCC in Epicel-treated patients were reported to Vericel or reported in the literature from the initial PAC presentation through October 31, 2021. In the reporting period of this PAC review, October 1, 2021 to September 30, 2022, the sponsor cumulatively identified a total of 13 cases of SCC in burn patients treated with Epicel (Table A in Appendix). Of the 13 cases, 5 were the old cases reviewed during the initial PAC presentation on March 7, 2017, and 8 were new cases identified in this review period, including one spontaneous report and 7 literature cases from a literature review conducted by the sponsor in 2022. Of the 11 patients reporting demographic/clinical data, 9 patients (81.8%) were males with SCC located on the lower extremities. Five patients (45.5%) were pediatric patients at the time of Epicel treatment. All burn injuries were catastrophic burns involving a total body surface area (TBSA) ranging from 70% to 99%. The latency period from Epicel use to occurrence of SCC ranged from 11 to 23 years (median:15 years). Three patients died as result of the evolution of squamous cell carcinoma. As per the sponsor, the reporting rate of SCC has not "significantly changed since the calculations in 2011 and 2014." In 2014, the sponsor calculated the SCC reporting rate *as 0.33% with 95% CI (0.11 - 0.78),* based on 5 SCC cases and (b) (4) treated patients as of April 9, 2014. In 2022, the sponsor calculated the SCC reporting rate as *0.56% (95% CI: 0.2981 to 0.9574)* based on 13 SCC cases and (b) (4) patients treated as of June 2022.

Vericel continues to monitor for the occurrence of AEs, including SCC, through their routine pharmacovigilance activities, including collection and analysis of spontaneously reported AEs, monitoring of published literature, and the Epicel Medical Device Tracker (EMDT) database. For the EMDT, Vericel contacts patients at least annually to update their contact and survival information for all patients treated with Epicel since 2007.

Reviewer comments: The cumulative reporting rate has increased from 0.33% (2014) to 0.56% (2022) with 13 total SCC cases reported by the manufacturer, 7 of which were from literature reports from an updated literature review conducted in 2021 – 2022 (please see appendix). This updated literature review included older publications from 2012 and 2013, in addition to a recent publication from 2021. Many of the cases contributing to the increase in the cumulative reporting rate had occurred prior to the annual reporting period. The manufacturer calculated p-values with the reporting rates

[2] Note that Epicel label includes an additional case of SCC in a patient with epidermolysis bullosa dystrophica (DEB).

and stated that the “rate is not significantly different,” from the reporting rate calculated in 2014. Given the limitations of passive surveillance data, most notably under-reporting, statistical inferences comparing reporting rates should be viewed with caution.

Though the cumulative reporting rate has increased, with the addition of 8 new reports in the annual reporting period, it is important to note that the reporting rate does not exceed the background rate of SCC from burn wound scars. SCC is the most common skin cancer to develop from burn wound scars, with an estimated 2% of burn scars undergoing malignant transformation.[3,4] Other sources have reported background rates of SCC in burn patients as ranging from 0.24%[5] to 6.97%[6]. As described in the label, in the reported Epicel cases, the SCC occurred in the grafted areas 11 to 23 years after Epicel grafting, while a longer latency period of 11 to 41 years (median 28) has been reported from the time of burn injuries to occurrence of SCC. When considering reporting rates for SCC, it is also important to note that the long latency period of SCC following CEA use; with continued product use over time and longer periods of exposure since treatment, more data is accumulating on the postmarketing experience for patients who were treated more than 10 years ago. Based on the AE reports, the patient population treated with Epicel have sustained massive burn injuries (often >90% TBSA burn injuries), and it is unknown if the severity of the burn injuries and number of Epicel grafts used, have an impact on the occurrence of SCC. The label was appropriately updated in 2022 with new information on the risk of SCC, a known and labeled risk for Epicel. The benefit/risk balance for Epicel remains favorable.

XII. SUMMARY

The number of death reports and types of AEs observed during this annual review period are similar to those listed in the IFU, and do not suggest new safety concerns. Infection and multi-organ failure are common in severe burn injuries, and the AEs reported during this reporting period represent outcomes consistent with the known comorbidities seen in severe burn injury patients. Given the high fatality rate in patients with severe burns, the number of reported deaths after Epicel use does not suggest a concern for fatal outcomes related to the device itself, as opposed to the underlying injury. High TBSA burn injuries in these cases is associated with a high fatality rate, even among patients who survive long enough to receive Epicel grafts. The 2022 cumulative reporting rate of SCC shows an increase from 2014 but does not exceed the reported background rates of SCC in burn scars in literature. The Epicel label was revised to include updated information on SCC latency period.

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[3] Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns. 2005 Jun;31(4):403-13.

[4] Gül U, Kiliç A. Squamous cell carcinoma developing on burn scar. Ann Plast Surg. 2006 Apr;56(4):406-8.

[5] Bernt Lindelöf, Britta Krynitz, Fredrik Granath et al. Burn Injuries and Skin Cancer: A Population-based Cohort Study. Acta Derm Venereol 2008; 88: 20–22

[6] Khalifa E. Sharquie and Raed I. Jabbar. The Frequency of Squamous Cell Carcinoma Among Patients with Long Standing Burn Scars. J Turk Acad Dermatol 2021;15(3):65-68

FDA did not identify any new safety signals during this comprehensive safety review of the manufacturer's Epicel HDE annual report, the MDRs received by FDA, and the literature published during the annual review period. The HDE for this device remains appropriate for the adult and pediatric populations for which it was granted. FDA will continue routine monitoring of the safety and distribution data for this device.

Appendix A

Table A. Cases of Squamous Cell Carcinoma After Epicel-Treated Burn Injury (n=13)

Case ID Date Report Received Source	Patient/Burn Information		Year of CEA Graft	Skin Cancer Information		Latency	Outcome
	Age, Sex	TBSA		Age at Dx (Year)	Location		
(b) (6) 25-Apr-2011 Literature (Theopold 2004)	34y, Male	95%	1989	~47y	Left leg	13y6mo	Recovered (30-Sep-2015)
(b) (6) 21-Apr-2011 Spontaneous	8y, Male	99%	1998	~20y (10-May-2010)	L abdominal wall, L knee, foot	11y10mo	Death (29-Apr-2011)
(b) (6) 26-Apr-2012 Spontaneous	Unknown Female	Unknown	1997	Unknown	SCC	~15y	"Alive and well" (29-May-2012)
(b) (6) 26-Apr-2012 Spontaneous	Unknown, Male	Unknown	1993	Unknown	SCC	~19y	Death (date unknown)
(b) (6) 17-Sep-2014 Spontaneous	46y, Male	95%	1998	~58y (Feb-2011)	Left knee	12y8mo	Recovered (22-Sep-2014)
(b) (6) 23-Aug-2022 Spontaneous	Unknown (adult); Male	95%	2011	Unknown (Aug-2022)	Leg	~11y	Ongoing (Aug-2022)
NA 2022 Literature	~18y Male	92%	1992	32y (Jun-2006)	Left thigh	14y	Recovered

Case ID Date Report Received Source	Patient/Burn Information		Year of CEA Graft	Skin Cancer Information		Latency	Outcome
	Age, Sex	TBSA		Age at Dx (Year)	Location		
(Baus 2021)							
NA 2022 Literature (Baus 2021)	~21y Male	80%	1995	40y (Oct-2014)	Left thigh	19y	Recovered
(b) (6) 2022 Literature (Baus 2021)	~17y Male	~70%	1998	33y (Feb-2014)	Left and right flank	16y	Death (Dec-2014)
NA 2022 Literature (Baus 2021)	~40y Male	90%	2001	54y (2015)	Right leg	~14y	Ongoing (Dec-2021)
					Left hip	~16y	
					Left thigh	~17y	
NA 2022 Literature (Bocchi 2013)	18y Female	95%, (87% 3rd degree)	~1990	41y (Apr-2012)	Knee	22-23y	Ongoing (2012)
NA 2022 Literature abstract (Finnerty 2012)	NA	NA	NA	NA	NA	NA	Unknown
NA 2022 Literature abstract (Finnerty 2012)	NA	NA	NA	NA	NA	NA	Unknown

Appendix B: Excerpt from Epicel Instructions for Use (Revision 11, dated November 2022)

WARNINGS

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.[7] [8]

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.

[7] Kowal-Vern A, Criswell BK. Burn scar neoplasms: literature review and statistical analysis. Burns. 2005. 31: 403-413.

[8] 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.

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Theopold C, Hoeller D, Velander P, Demling R, Eriksson E. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. Plast Reconstr Surg. 2004 Oct;114(5):1215-1219.