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 990200/94
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.)
- 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 (see section VII).

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 2022: (b) (4) Epicel grafts, including 2055 grafts in pediatric patients.
- Calendar year 2023: Not yet available, however, from January 1, 2023 through September 30, 2023, Vericel distributed (b) (4) Epicel grafts, including 1462 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, 2022 to September 30, 2023, 19 pediatric patients, (b) (4) adult patients, and (b) (4) of unknown age were treated with Epicel for burn injuries.

VII. LABEL CHANGES IN REVIEW PERIOD

There was a label change during the PAC review period (October 1, 2022, to September 30, 2023). 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. Although this labeling update was approved shortly after the previous PAC period (Oct 2021 to Sep 2022), it was also included in last year's Epicel Annual Safety Update Memorandum for the PAC. 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 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 December 4, 2023, to identify postmarket adverse event reports associated with the use of Epicel submitted to FDA during the annual review period, October 1, 2022, to September 30, 2023. The search identified two (2) MDRs, including one (1) report with fatal outcome, and one (1) report with serious injury.

No reports involved pediatric patient(s). Both reports were submitted by the manufacturer. The patient with fatal outcome had extensive third degree burns and died after grafting. As per the manufacturer's assessment, the death was probably related to the underlying condition. The summary of death and injury reports is displayed in Table 1.

Table 1. Summary of Death and Injury Reports (n = 2)

Case ID	Age (year)	Sex	Event	Time from Graft to Event	PT
US-VCEL-(b) (6)	41	Male	Serious injury	15 years and 24 years	Squamous Cell Carcinoma
US-VCEL-(b) (6)	55	Male	Death	Same day	Unknown

* This patient received Epicel grafts on (b) (6), 1999, and experienced SCC of the right lower extremity anterior shin area on two separate occasions in 2014 and 2023 respectively. Please see case details in Section IX (Annual Report Review).

Reviewer comment: The report of death in the patient who sustained extensive third degree burns and died the same day as grafting is consistent with complications experienced by severe burn trauma patients in the intensive care setting. Squamous cell carcinoma is a known risk for Epicel and the label includes a Warning to further describe SCC reports following Epicel. The number of cases does not exceed the annual background occurrence of cases due to other causes. No new safety concerns were identified.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (September 1, 2022, to August 31, 2023) was reviewed. During the reporting period, a total of 76 events (38 serious events, 38 nonserious events) were reported in 39 patients.

The most frequently reported system organ class (SOC) categories during this reporting period were: Product Issues (30.2%; 23/76); General Disorders and Administration Site Conditions (21.1%, 16/76); Injury, poisoning and procedural complications (11.8%, 9/76); Infections and infestations (7.9%, 6/76); Respiratory, thoracic, and mediastinal disorders (5.3%, 4/76); and Gastrointestinal disorders (5.3%, 4/76). Of the 76 reports, 14 reports involved fatal outcomes, of which there were 12 adult reports, one (1) pediatric report, and one (1) report that occurred in a patient of unknown age.

Pediatric Death Reports: There was one (1) report with fatal outcome in pediatric Epicel recipient. The patient was a 7-year-old boy with burns of 85% TBSA. The patient had three Epicel gratings on November, 29, 2022 (31 grafts), January 3, 2023 (20

grafts), and January 24, 2023 (35 grafts), respectively. The patient died due to septic shock on February 21, 2023.

Adult Death Reports: The sponsor received 13 reports involving fatal outcomes in adult Epicel recipients or Epicel recipients of unknown age during the reporting period of the Annual Report. These 13 cases, including one (1) case identified in the MDR database (described in section VIII.B), are displayed in Table 2.

Table 2: 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
US-VCEL-(b) (6)	75 Male	Death	unknown	Unknown
US-VCEL-(b) (6)	42 Male	Sepsis	-33 days	Sepsis
US-VCEL-(b) (6)	unknown Male	Infection	unknown	Infection
US-VCEL-(b) (6)	48 Female	Death	20 days	Unknown
US-VCEL-(b) (6)	50 Male	Death	59 days	Unknown
US-VCEL-(b) (6)	38 Male	Sepsis	unknown	Unknown
US-VCEL-(b) (6)	74 Male	Death	unknown	Unknown
S-VCEL(b) (6)	55 Male	Death	unknown	Unknown
US-VCEL-(b) (6)	22 Female	Obstructive airways disorder	unknown	Obstructive airways disorder
US-VCEL-(b) (6)	29 Male	Death	unknown	Unknown
US-VCEL-(b) (6)	26 unknown	Stroke	unknown	Unknown
US-VCEL-(b) (6)	41 unknown	Gastrointestinal haemorrhage	unknown	Unknown

Case ID	Age Sex	Event	Time from Graft to Event	Cause of Death
US-VCEL-(b) (6)	24 unknown	Myocardial infarction	unknown	Unknown

*Cases initially reported prior to the PAC reporting period; the sponsor submitted follow-up reports on these cases during this PAC annual review period.

** Case reported as MDR

Reviewer comment: The reports of death for which information on cause of death was available were related to cardiac events or sepsis, which are known complications with underlying burn injuries.

Squamous Cell Carcinoma (SCC): The sponsor's Annual Report included one (1) report of SCC in an adult patient. The patient was a 41-year-old male who had Epicel grafting on (b) (6) , 1999. The patient experienced SCC of the right lower extremity anterior shin area on two separate occasions. The first occasion was an episode of SCC diagnosed in (b) (6) 2014. The second occasion was development of SCC in the same location in (b) (6) 2023. The affected area was excised in (b) (6) 2023 with clean margins noted. Both occurrences were reported to FDA as an MDR in April 2023.

Product Issue Reports: There were 21 cases associated with 23 reported events of Product Issues in the Annual Report (one case was associated with three events). These reports were not reported as MDRs to FDA. Twenty-one (21) cases are summarized in the table 3 below.

Table 3. Summary of Product Issue Reports (n=21)

Case ID	Lot#	# Grafts utilized	# Grafts not utilized	Product Issue Reported
US-VCEL-(b) (6)	EE03036	66	6	Product was refrigerated at the site
US-VCEL-(b) (6)	EE03040A	84	0	Product was refrigerated at the site
US-VCEL-(b) (6)	EE03036A	80	2	Product was refrigerated at the site
US-VCEL-(b) (6)	EE03056	69	10	Skin floating in the graft dish
US-VCEL-(b) (6)	EE03096	70	6	Skin floating or not properly attached to gauze
US-VCEL-(b) (6)	EE03095	32	9	Skin detached from backing /floating cells
US-VCEL-(b) (6)	EE03084B	34	4	Skin detached from backings

Case ID	Lot#	# Grafts utilized	# Grafts not utilized	Product Issue Reported
US-VCEL-(b) (6)	EE03108	85	10	Skin floating or not properly attached to the gauze backing
US-VCEL-(b) (6)	EE03116	60	6	Skin floating or not properly attached to gauze
US-VCEL-(b) (6)	EE03112	60	12	Grafts were rolled up and unsecured to gauze
US-VCEL-(b) (6)	EE03108A	100	20	Grafts sheared from backings and unusable
US-VCEL-(b) (6)	EE03095B	0	35	10 grafts detached from backing.
US-VCEL-(b) (6)	EE03125	109	44	44 grafts not usable, cells detached and scalloped
US-VCEL-(b) (6)	EE03116A	31	2	Grafts detached from backings
US-VCEL-(b) (6)	EE03108B	80	22	Grafts detached from backings
US-VCEL-(b) (6)	EE03094C	30	41	One graft scalloped, two leaks, broken seal
US-VCEL-(b) (6)	EE03108C	60	33	Grafts detached from backings
US-VCEL-(b) (6)	EE03137	92	2	Grafts detached from backings
US-VCEL-(b) (6)	EE03141	101	1	Scalloped graft
US-VCEL-(b) (6)	EE03152	26	9	Detached skin Floating in media
US-VCEL-(b) (6)	EE03156	60	12	Scalloped and/or floating skin

***** Three events were associated with one case

Reviewer comments: Eighteen of the 23 product issue events were related to graft floating/detachment from the backing. In the remaining reports, three were temperature excursion issues (product was refrigerated at the site), one was product leakage and broken seal. In response to an information request, the sponsor stated: the root cause of graft detachment was determined to be multifactorial. Firstly, (b) (4) Secondly, the petrolatum gauze packs used to prepare the Epicel skin grafts were being supplied with (b) (4) rendering the grafts

unusable. As a corrective action, (b) (4)

Regarding the product leakage, the root cause was (b) (4) resulting in media leaking from the dish. As a corrective action, (b) (4)

. The detached grafts were not used on patients, and no clinical adverse events were reported for these patients.

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on December 5, 2023, 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, 2022, and September 30, 2023, retrieved 14 articles. Titles and abstracts were reviewed for relevance to safety information specifically for Epicel device and its labeled indication. One (1) article relevant to Epicel AEs was identified and is summarized in the table below.

Article	Clinical Summary
Homsombath B, Mullins RF, Brandigi C, Hassan Z, et al. Application and Management of Cultured Epidermal Autografts on Posterior Burns-A 5-Year, Multicenter, Retrospective Review of Outcomes. *J Burn Care Res*. 2023 Jan 5;44(1):170-178.	Data in 40 patients with mean TBSA of 56% demonstrated a high rate of successful cultured epidermal autografts (CEA) engraftment (83%), and overall survival rate (90%) following one or two applications with CEA and/or CEA + split thickness skin graft.

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 2021. In 2022, the Sponsor conducted an updated assessment for SCC, including spontaneous reports and literature case reports, and cumulatively identified a total of 13[3] cases of SCC in burn patients treated with Epicel (please see prior annual PAC update memo under BH 990200/92). Five of the 13 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). In the current annual review period, there was one (1) new report of SCC (US-VCEL-(b) (6) , see Table 1). (Please see Appendix A for updated case count of SCC cases).

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. FDA is monitoring SCC occurrence in Epicel-treated patients through MDRs, annual reports from the manufacturer, periodic literature review, and annual PAC reviews.

Reviewer comments: As part of the sponsor's 2022 assessment of SCC in epicel-treated patients, the cumulative reporting rate of SCC (based on 13 SCC cases reported and (b) (4) patients treated as of June 2022) was calculated to be 0.56%. This reporting rate does not exceed the background rate of SCC in patients with burn wound scars, with an estimated 2% of burn scars undergoing malignant transformation.[4,5]

[2] Note that Epicel label includes an additional case of SCC in a patient with epidermolysis bullosa dystrophica (DEB).
[3] Of the 13 cases, 5 were the old cases reviewed during the initial PAC presentation on March 7, 2017, one was a new case reported to Vericel in 2022, and 7 were literature cases from the literature review conducted by the sponsor in 2022.
[4] Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns. 2005 Jun;31(4):403-13.
[5] Gül U, Kiliç A. Squamous cell carcinoma developing on burn scar. Ann Plast Surg. 2006 Apr;56(4):406-8.

Other sources have reported background rates of SCC in burn patients as ranging from 0.24%[6] to 6.97%[7].

In the current annual interval (subject of this 2024 annual PAC review memorandum), there was one additional report of SCC. This additional case does not substantially change the cumulative reporting rate of SCC in Epicel-treated patients, as compared to the background rate of SCC from burn wound scars.

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, with the long latency period of SCC following CEA use and 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. 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 is common in severe burn injuries, and this as well as other 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.

On November 18, 2022, the Epicel label was revised to include updated information on SCC latency period, and as described in the review for the labeling supplement and the prior 2023 PAC annual update memo, the cumulative reporting rate of SCC does not exceed the reported background rates of SCC in burn scars in literature. Since the 2022 label change, there has been one additional report of SCC during the safety review period.

[6] 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

[7] 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 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=14)

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		
VCEL-2011(b) (6) 25-Apr-2011 Literature (Theopold 2004)	34y Male	95%	1989	~47y	Left leg	13y6mo	Recovered (30-Sep-2015)
-VCEL-2011(b) (6) 21-Apr-2011 Spontaneous	8y Male	99%	1998	~20y (10-May-2010)	L abdominal wall, L knee, foot	11y10mo	Death (b) (6)
VCEL-2012(b) (6) 26-Apr-2012 Spontaneous	Unknown Female	Unknown	1997	Unknown	SCC	~15y	"Alive and well" (29-May-2012)
VCEL-2012-(b) (6) 26-Apr-2012 Spontaneous	Unknown Male	Unknown	1993	Unknown	SCC	~19y	Death (date unknown)
VCEL-2014-(b) (6) 17-Sep-2014 Spontaneous	46y Male	95%	1998	~58y (Feb-2011)	Left knee	12y8mo	Recovered (22-Sep-2014)
VCEL-22-(b) (6) 23-Aug-2022 Spontaneous	Unknown (adult) Male	95%	2011	Unknown (Aug-2022)	Leg	~11y	Ongoing (Aug-2022)
VCEL-23-(b) (6) 22-Apr-2023	41y Male	Unknown	1999	41y (2023)	Right lower extremity anterior shin area	15y	Ongoing (Apr-2023)

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		
Spontaneous					Right lower extremity anterior shin area	24y	
NA 2022 Literature (Baus 2021)	~18y Male	92%	1992	32y (Jun-2006)	Left thigh	14y	Recovered
NA 2022 Literature (Baus 2021)	~21y Male	80%	1995	40y (Oct-2014)	Left thigh	19y	Recovered
FR-VCEL-(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.[8,9]

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.

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

[9] 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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Bocchi F, Zermani R. Report of a case of Marjolin's Ulcer in a patient with multiple burn scars during plastic surgical treatment: surgical resolution aimed at maintaining functional knee. Acta Biomed. 2013 Jun 1;84(1):61-63.

Finnerty C, McCauley R, Hawkins H, Herndon D. Genomic alterations in cultured epithelial autograft (CEA) associated with the development of squamous cell carcinoma. J Tissue Eng Regen Med. 2012; 6(suppl.1):94.

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.