FDA Executive Summary

Epicel
(cultured epidermal autografts)
HDE# BH990200

Annual Pediatric Safety Update for the Pediatric Advisory Committee

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a 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. According to the Epicel Directions for Use (DFU), the mouse 3T3 fibroblast feeder cells have been extensively tested for the presence of infectious agents, including sterility testing for bacterial and fungal contamination, testing for mycoplasma contamination, and screening for viral and retroviral contaminants. During manufacturing, Epicel is evaluated for sterility via sterility assessments conducted pre-release and 14-days post-release. Reagents used in the manufacture of Epicel are also tested for sterility and endotoxin content.

IV. REGULATORY HISTORY

- 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated product.

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

- 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 the CDRH to CBER.
- 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 of 2017.

V. PEDIATRIC USE

Since marketing approval in 2007, as a Humanitarian Device Exemption (HDE), for use as wound covering in patients who have deep dermal or full thickness burns in >30% of body surface area, and approximately 29% of patients treated with Epicel worldwide were pediatric patients (age<22). 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.

VI. ANNUAL DISTRIBUTION NUMBER/ANNUAL SALES NUMBERS

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (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 per year from 2008 through 2014 (Review Memo BH990200/34, ADN calculation, Feb. 18, 2016); 4000 represents the target population per the HDE definition at the time the pediatric labeling was approved (February 2016).

The number of Epicel grafts distributed during this reporting period (10/1/2016 through 9/30/2017) has not exceeded the ADN. During this period, (b) (4) pediatric patients were treated with Epicel for burn injuries. Note: These estimates were provided by the manufacturer for FDA review. Dose distribution data is protected as confidential commercial information and may require redaction from this review.

VII. 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 effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations;
  - off-label use; and use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified and/or additionally biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other 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 a specific event can be difficult based solely on information provided in a given report. 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, attributable to potential causes such as reporting practice, 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 Oct. 10, 2017, to identify all existing post market

adverse event reports associated with the use of the Epicel submitted to FDA from 10/1/2016 through 9/30/2017. The search resulted in the identification of 6 MDRs. One of these reports was previously reported in 2011 and did not contain any new information, so it is not included in this review. All 5 of the remaining unique reports involved deaths in patients who received Epicel. All 5 reports were submitted by the manufacturer.

Pediatric MDR
Only one report involved a pediatric patient. A 2-year-old female patient received Epicel for 85% TBSA burns. The patient died from an unknown cause 19 days after grafting with Epicel. Further details of this case were not provided.

Adult MDRs
Three of the four adult patients were victims of burn injury with TBSA ranging from 85% to 95% (mean=92%). The 4th patient was an 86-year-old male who was grafted with Epicel for treatment of an unspecified injury and subsequently died of multi-organ failure. The manufacture's narrative stated that the deaths/adverse events were unrelated to the use of Epicel. Table 1 provides a summary of all 5 reports.

Table 1. Summary of Death Reports (n=5)

MDR Report Number	Age (Yrs)	Sex	TBSA (%)	Grafting Information	Time of Graft to Death	Cause of Death
1226230-2017-00002	2	F	85%	16 units grafts in 2017	19 days after graft	Unknown cause
1226230-2017-00006	42	M	95%	40 units grafts in 2017	44 days after graft	Multi-organ failure
1226230-2017-00007	30	M	95%	48 units grafts in 2017	33 days after graft	Sepsis and systemic infection
1226230-2017-00008	31	M	93%	48 units grafts in 2017	22 days after graft	Unknown cause
1226230-2017-00001	86	M	UNK	40 units grafts in 2017	8 days after graft	Multi-organ failure

VIII. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (reporting period 8/31/2016-9/1/2017) was reviewed. During the reporting period, the sponsor received 15 initial case reports which included a total of 35 serious and 10 nonserious adverse events terms.

The most common AEs in these cases were infection (N=7), followed by multiple organ dysfunction syndrome (N=4) and death (N=3). Of the 15 cases, 10 involved deaths, including 5 pediatric and 5 adult cases.

Pediatric Death Reports
The sponsor received 5 reports involving a fatal outcome in pediatric Epicel recipients during the reporting period of the Annual Report. These 5 cases, which include the 2-year-old identified in the MDRs and described above, are displayed in Table 2.

Table 2: Pediatric Case Reports Received by the Sponsor During the Reporting Period with a Fatal Outcome

Case Identifier	Patient Demographics	TBSA (%)	Grafting	Time of Graft to Death (day)	Cause of Death/ Event Terms
(b) (6)	2 years Female	85%	16 grafts of Epicel.	19	Death unknown cause
(b) (6)	7 years Male	93%	48 units of Epicel	1 month	Heart Failure
(b) (6)	14 years Male	84%	6 times with a total of 180 grafts	UNK	Respiratory arrest Congestive cardiomyopathy
(b) (6)	15 years Female	60%	144 grafts of Epicel.	UNK	Multiple organ dysfunction syndrome Infection
(b) (6)	21 years Male	UNK	59 grafts of Epicel.	362	Death unknown cause

Note*= case has been reported to MDR

Adult Death Reports
Four of the five adult death reports were previously identified in the MDRs and are discussed above. The additional case described in the Annual report is a 65-year-old male with 69% TBSA who died 10 days after grafting due to multiple organ dysfunction syndrome.

The majority of reports of death following Epicel treatment were related to multiple organ dysfunction or sepsis. According to the reporter in each case, none of the deaths were reported as related to use of Epicel. A review of the AE data revealed that the nature and type of reported AEs received during this reporting period were similar to those reported in the previous Epicel Annual Reports and those listed in the Epicel DFU. The AEs reported are consistent with those experienced within the natural course of severe burn trauma patients in intensive care settings.

IX. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 30, 2017 using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" for articles published between 10/1/2016 and 9/30/2017 retrieved 5 articles. Titles and abstracts were reviewed for relevance to safety information specifically for the Epicel device and its labeled indication. The 5 publications included 4 articles on basic science/methodology and 1 general subject review. None of the 5 articles were specific to Epicel and none of the 5 articles contained reports of adverse events or other safety information for Epicel.

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

Squamous cell carcinoma (SCC) is the most common skin cancer to develop from burn wound scars. There have been no new cases of SCC in Epicel-treated patients reported to Vericel or reported in the literature since the data-lock date of the initial PAC presentation for Epicel (September 30, 2016), up to October 17, 2017. (The 6 cases of SCC observed in Epicel-treated patients since the first use of Epicel in 1988 were reviewed and discussed during the initial PAC presentation). 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). For the EMDT, Vericel contacts patients at least annually to update their contact and survival information for all patients treated with Epicel since 2007.

XI. SUMMARY

The number of death reports and types of AEs observed in this reporting period are similar to those observed during the previous PAC evaluation and those listed in the DFU, and do not suggest new safety concerns. Infection and multi-organ failure are common in severe burn injuries, so the AEs reported represent outcomes that would be expected in patients with these injuries, particularly with such high TBSA involved. 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. Again, the extremely high TBSA in these cases is associated with a high fatality rate, even among patients who survive long enough to receive Epicel grafts.

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