Reviewer: Yao-Yao Zhu, M.D., Ph.D.

Branch Chief: Ilan Irony, M.D.

Date of Review Completion: June 12, 2014

Executive Summary: This review evaluates special labeling supplement 21 for the Genzyme's Epicel HDE to finalize the labeling language in three documents (a. Directions for Use; b. Patient Information; and c. Dear Health Care Provider Letter) regarding new reports of cutaneous squamous cell cancer (SCC). Epicel, an autologous cultured epidermal autograft, was approved by CDRH in 2007 to treat patients who have deep dermal or full thickness burns comprising a total body surface area (TBSA) $\geq$30%. A total of 1,500 burn patients received Epicel since 1988, and four new cases of SCC were reported since approval. Some aggressive features of SCC in these reports are concerning: multi-centric location, large size, rapid locoregional metastasis, shorter latency period, and serious/fatal outcomes. In supplement 21, the applicant provided revised physician label and Patient Information based on the updated information, and a Dear Health Care Provider (DHCP) Letter for FDA review. Many changes were made in these three documents by a joint effort from clinical, CMC, and APLB teams. . In Supplement 21, A1 as communicated by email, Genzyme accepted all FDA's revisions and provided final labels.

Recommendations: the review recommends approval of the revised labels. The reviewer recommends additional minor edits in label format:

1. Direction for Use: the 2nd header in the Clinical Information can just be "Munster Study [2]"
2. Patient Information: Four missing questions marks: please add question marks after four subtitles without question marks (3^{rd}, 4^{th}, 6^{th}, 8^{th})

Discussion of FDA Labeling Revision: clinical team perspective

Physician label: Direction for Use

The main change is the descriptive language of SCC under the Precaution section and Adverse Reaction section. To provide a full description of these reported SCC in Epicel recipients, based on MedWatch reports and literature description of SCC (Table 1 and reference 4 &9), the reviewer added "large size, aggressive growth, local recurrence after resection, and fatal outcome in some of the cases" in addition to "multi-centric location" as the only feature described by the applicant. The reviewer revised the statement - "shorter time-to-occurrence of approximately 12 years from time of grafting" to provide a description of the latency in SCC and a statement of average latency in the literature (Reference 8). The reviewer deleted the statement "Genzyme epidemiologic review suggests that the estimated post market reporting rate of SCC in Epicel treated patients exceeds the background rate of 2.5/1000". The Division of Epidemiology suggested that the calculated background rate is inconclusive and MedWatch cases often times are under-reported.

Other changes:

- Simplify the subtitles under Clinical Information.
- Change sentence structure to imperative sentence for easy reading under Graft Application

Patient Information

The reviewer adopted a "question" and "answer" format for the entire writing. Some sentences were modified to plain language.

Dear Health Care Provider Letter (DHCP)

The reviewer did following changes based on recent FDA Guidance for DHCP Letter published in 2014 (Guidance for Industry and FDA Staff Dear Health Care Provider Letters: Improving Communication of Important Safety Information):

- Change subject title from "Important updates to product information" to "Important drug warning" based on FDA Guidance.
- Change the descriptive language for SCC (same as in other two documents)
- Delete other irrelevant new product information such as HDE number and change in surgical clip material, which may distract from the main issue of SCC.

CLINICAL REVIEW OF HDE 990200-21 FOR SPECIAL LABELING SUPPLEMENT – CHANGE BEING EFFECTED

Applicant: Genzyme

Product: Epicel: cultured epidermal autographs

Approved Use: Treatment of patients who have deep dermal or full thickness burns comprising a total body surface area greater than or equal to 30%

Submission Date: May 14, 2014

Other submission referenced:
H990002/S13, a 75-day supplement submitted to CDRH on October 18, 2011, with proposed label changes.
H990200/S19, filed with CBER on February 24, 2014, with similar content as S13; CBER requested updated information be provided.

Review clock: due date: June 19, 2014

Regulatory Background

Epicel, a cellular product of cultured epidermal autografts, was approved as an HDE device October 25, 2007 by CDRH for treatment of patients who have deep dermal or full

thickness burns comprising a total body surface area greater than or equal to 30%. In 2013 this HDE was transferred from CDRH to CBER with HDE number changed from H990002 to BH990200.

The applicant initially filed a supplement S-13 with CDRH on October 18, 2011 to support a label change for Epicel following a report of serious adverse event in April 2011 regarding a case of squamous Cell Carcinoma (SCC) in a patient who had received Epicel in 1998. Although squamous cell cancer is the most common skin cancer for burn wound scar, the reported event has concerning features ofmulti-centric in presentation and aggressive growth, and presented slightly earlier than what had been previously reported in burn wounds not treated with Epicel. . After a thorough evaluation, Genzyme determined that changes to the Epicel label are warranted, to add a precaution and include information about adverse reactions.

The applicant filed supplement S-19 to CBER in February 2014 to request labeling changes. CBER requested updated information.

The applicant submitted supplement S-21 May 2014 to update information regarding SCC.

Review of five cases of squamous cell cancers related to the use of Epicel

Case 1. Described in the current label reference for SCC

A patient with diagnosis of epidermolysis bullosa dystrophica (DEB) had a chronic non-healing ulcer. The patient underwent dermabrasion in preparation for grafting, and was treated with Epicel in 1994. A few days later, the grafted area appeared to be covered with a papillomatous growth. The area was biopsied and the biopsy specimen was determined to be a SCC, noted to be a common occurrence in patients with epidermolysis bullosa of the dystrophic variety. A specimen of the patient's graft did not cause tumor formation in nude mice; however, no definitive diagnosis was made from the biopsy. Six weeks later, the cancer had extended to all margins and to bone. The patient's leg was amputated below the knee on 31 May 1994.

Reviewer comments: the concerning features in this case is the rapid development of SCC a few days after application of Epicel and serious outcome of amputation. SCC is a known risk for DEB, but the aggressive features in this case are uncommon.

Case 2. The Index case for the proposed labeling change
An eight-year old boy, suffering a 99% TBSA burn, received Epicel grafts on 3 occasions in 1998. The patient noticed a growth on his abdomen for about 6 months that appeared to be growing larger. He presented to the hospital on 10 May 2010 (12 years after receiving Epicel) with a very large, well differentiated squamous cell cancer (SCC) over the left abdominal wall. After treatment, including resection and coverage with skin grafts, a subsequent CT scan showed a mass in the patient's left knee as well as a mass in the epigastric region. The patient expired on (b) (6) . The patient was treated with

insulin-like growth factor (IGF-1) and insulin- like growth factor binding proteins (IGFBP-3) for 6 days between 15 August 1998 and 20 August 1998, during the time of treatment with Epicel.

The physician described three features of the SCC that were of concern to him: first, the SCC was multicentric in its presentation, appearing in the abdomen, the knee, and the foot (not previously reported), rather than at a single site ; second, the timing of the SCC was more accelerated and sooner thanthe average reported for diagnosed SCC after a burn injury; third, the histopathology of this SCC was extremely aggressive and atypical in features, including altered P53. The physician also questioned the use of the cholera toxin and epidermal growth factor in the manufacture of Epicel. In a publication of meeting abstraction (reference 4), this physician described three cases of SCC development after Epicel use.

Reviewer's Comments: concerning features of this case: multicentric, large, local invasion, recurrence, and fatal. SCC in Epicel recipients may be under-reported. The treating physician only reported one case instead of three.

Case 3. Publication by Theopold et al 2004, entitled *Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft*.
A 34 year-old man who sustained 95% TBSA burn around 1990 received cultured epidermal autografts (CEA). Thirteen years and 6 months after the initial grafting, the patient developed 5 distinct lesions of SCC in some of the grafted areas of the left leg. The physician confirmed that this patient also received Epicel treatment.

Reviewer's Comment: recurrent theme of SCC in Epicel user: extensive burns, multi-focal location, and shorter latency.

Case 4 and 5: Two cases of squamous cell cancers were reported in April 2012 by the same physician. Patients received Epicel in 1993 and 1997; one patient died from respiratory failure and the other patient was well and alive. The relationship between death and Epicel use is unknown.

Table 1. Summary of Five Cases of Squamous Cell Cancers

	Case 1	Case 2	Case 3	Case 4	Case 5
Dx	DEB	99% TBSA burn	95% TBSA burn	No detail	No detail
Source	Literature	MedWatch	Literature search	MedWatch	MedWatch
Treatment	Epicel	Epicel	Epicel	Epicel	Epicel
Age at Grafting	unknown	8 yo (1998)	34 yo (1989)	Grafted in 1997	Grated in 1993
Onset of SCC after grafting	A few days	12 years (2011)	13.5 years	15 yrs.; Reported in 2012	19 yers?
Lot Info		(b) (6) Met all release criteria		Epicel lot (b) (6) Met all release criteria	
Location of	Lower extremity	Left abdominal wall,	Five distinctive	unknown	unknown

SCC		left knee, epigastric region, foot	SCC lesions on left leg within 7 months		
Outcome	Amputation due to extension of SCC to all margins and to bone	fatal	Recovered	Alive and well	Fatal
Pathology	Papillomatous growth	Extremely aggressive, atypical in features with altered P53	Well-differentiated SCC	Not reported	Not reported
Concurrent therapy	unknown	IGF-1 and IGFBP-3 were used for 6 days during the year of burn treatment	unknown	Not reported	Not reported

DEB: epidermolysis bullosa dystrophica; SCC: squamous cell cancer; TBSA: total body surface area

Reviewer's Comments: several features in the five SCC cases are of concerns: aggressive features: large size, multi-focal, locoregional metastasis, and serious/ fatal outcomes (two deaths and one amputation). Shorter latency: 12 and 13 years in cases 2 and 3 as compared with 30 years in average burn scars (Reference 8). Does the product manufacturing process contribute to these findings, such as cholera toxin, epidermal growth factors, and 3T3 murine feeder cells? CMC and preclinical input are needed. In the label, these features should be described, and vigilant cancer surveillance should be emphasized.

Review of Frequency of SCC in Epicel recipients vs. baseline background rate of SCC in normal population and in burn population

The rate of SCC in Epicel recipients is 0.33% with 95% CI (0.11, 0.78). The numerator is 5 cases of SCC reports and the denominator is 1494 of Epicel treated patients from 1988 to April, 9th, 2014.

The applicant estimated the background rate of SCC in burn patients equal to 0.26%. The background rates for burn >30% TBSA and >90% TBSA are similar.

Reviewer's Comments: Many case reports of burn scar cancer were published in the literature. However, two population cohort studies from Denmark and Sweden in burn patients (16,903 and 37,095 patients, respectively) did not find evidence for significantly increased risks for skin cancers on the burn wounds of follow-up (after up to 25 to 39 years, respectively). The same risks were found for both severe burn and mild burn (references 6 and 7).

The SCC by spontaneous reporting may be under reported. The estimated rate of SCC in Epicel recipients appears to be higher than background SCC rate, implicating an increased risk. These rate estimates are not stable, and one cannot draw strong conclusions in comparing background rates to the rate of occurrence after application

of this product. According to two cohort studies, risk of SCC does not increase in burn patients.

(OBE Consult by Meghna Alimchandari, M.D. - Overall Conclusions)

1. OBE/DE agrees with the overall method of calculation of the annual background rate of SCC in burn patients (S-013, section 4.3.1). However, the applicant should: a. cite reference for annual expected 160,000 SCC cases in US
b. if data available, consider only burn patients who are hospitalized as denominator to reflect serious burn injuries and capture potential cases eligible for Epicel
c. understand that the generalizability of 2% SCC occurring in burn patients to the current US population is unclear since this estimate is from a 1930 study [4]
d. Update with the 2014 National Burn Repository data for the denominator

2. OBE/DE does not agree with the applicant's calculation of background rate of SCC in burn patients ≥30% or ≥90% TBSA burns who are eligible to receive Epicel treatment (S-013, section 4.3.1).

3. OBE/DE does not agree with the applicant's calculation of rate of documented cases of SCC in Epicel patients (S-013, 4.3.2). The sponsor should update the rate of SCC in Epicel patients to include new data since 2011 submission of S-013.

4. OBE/DE recommends a case series analysis to better characterize the time-to-onset of SCC cases in Epicel patients (S-013, 4.3.3)

5. Additional data from the literature: The SCC incidence in hospitalized burn patients who were treated with skin transplant (calculated using the Danish study data) can be potentially used a background rate for this review. The concern, however, is the generalizability of this background incidence to the US population considering that the environmental and genetic risk factors for SCC may be different in the two populations.

References

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5. Wallingford SC et al. Skin cancer arising in scars: a systemic reviewer. Dermatol Surg. 2011; 37: 1239-1244

6. Mellemkjaer L et al. Risks for skin and other cancers up to 25 years after burn injuries. Epidemiology. 2006; 17: 668-73

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