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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

OCTOBER 2012

This e-alert is part of a series of monthly e-alerts summarizing publicly-available FDA enforcement letters (i.e., warning letters and untitled letters) relating to the advertising and promotion of drugs, biologics, and medical devices. In October 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letter on FDA's website:[1]

- Untitled letter to Genentech, Inc. re: Tarceva® (erlotinib) tablets (October 3, 2012) ("Genentech Untitled Letter")[2]

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) posted the following enforcement letter on FDA's website:

- Warning letter to CellTex Therapeutics Corporation re: adipose derived mesenchymal stem cells (AdMSC) product (September 24, 2012) ("CellTex Warning Letter")

The Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) posted the following letters on FDA's website:

- Warning letter to Acu-International Supplies, Inc. re: the Electro Meridian Imaging (EMI) device (September 25, 2012) ("Acu-International Warning Letter")
- Warning letter to PC Tan re: KBL Brand Devices – Mon Amie, Optima, and pureCollagen (October 10, 2012) ("PC Tan Warning Letter")

These letters raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded and/or adulterated.

This alert merely summarizes the allegations contained in FDA's letters, presented under the corresponding headings used by the agency in its letters. This alert does not contain any analysis, opinions, characterizations, or conclusions by or of Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any of its clients.

Genentech Untitled Letter

According to its prescribing information (PI), Tarceva is indicated as a monotherapy for "the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer

[1] Only enforcement letters posted to FDA's website in October 2012 are included herein. Letters issued in October but not posted to the website by October 31, 2012 will be summarized in our alerts for the months in which those letters are posted.

[2] The dates referenced for the letters are the issue dates.

whose disease has not progressed after four cycles of platinum-based first-line chemotherapy," and for "the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen." Tarceva is also indicated, in combination with gemcitabine, for "first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer." Tarceva is associated with several potentially fatal risks and numerous other adverse events, including rash, fatigue, and nausea. OPDP reviewed two visual aids—a pancreatic cancer visual aid, and a non-small cell lung cancer (NSCLC) visual aid—for Tarceva, and concluded that the visual aids contained misleading efficacy claims and minimized the drug's risks.

Misleading Efficacy Claims: The pancreatic cancer visual aid contained the following claims: "Retrospective data suggest Tarceva-related rash is associated with a clinical benefit[,]" and "[b]ased on a retrospective, exploratory analysis, a strong correlation was observed between the presence of rash and improved survival in the pivotal phase III clinical trial." The visual aid also presented a Kaplan-Meier graph comparing overall survival in patients who developed a grade 2+ rash during Tarceva + gemcitabine combination treatment versus gemcitabine monotherapy. The graph showed that the addition of Tarceva to gemcitabine produced a 3.7 month overall survival benefit in patients that develop a grade 2+ rash. According to Tarceva's PI, however, the addition of Tarceva to gemcitabine increased overall survival only by approximately 12 days in the indicated patient population. OPDP concluded that the presentation of median overall survival benefit in the Kaplan-Meier graph "drastically" overstated Tarceva's efficacy. OPDP stated further that "the development of rash and its correlation with [overall survival] were not pre-specified endpoints in the pivotal study. The data and subsequent claims presented in this sales aid were derived from a retrospective, exploratory subgroup analysis that does not provide substantial evidence to support the efficacy claims cited above." Additionally, OPDP found that these claims minimized Tarceva's risks "by portraying the adverse reaction of 'rash' as an efficacy predictor and therefore a potential benefit to patients."

OPDP also pointed to claims and graphs in the NSCLC visual aid that suggested the overall survival benefit from Tarceva extended to subgroups of patients with squamous cell carcinoma and adenocarcinoma. For example, one graph depicted a 5.6 month median overall survival in squamous cell carcinoma patients treated with Tarceva, versus a 3.6 month median for those given a placebo. OPDP concluded that claims of statistical significance were misleading because these claims were based on retrospective exploratory analyses and lacked prospective statistical design.

Overstatement of Efficacy: The front covers of the visual aids depicted a picture of an hourglass resting on its side labeled "Tarceva." An elderly person and a child sat inside the bottom half of the hourglass reading a book together. OPDP found that, together with the claim "[e]xtending survival for *moments that matter*,"[3] this presentation strongly suggested "that time is standing still for the cancer patient because of Tarceva therapy." OPDP explained that Tarceva's pivotal trials showed improvements in overall survival, but that these improvements "do not support the implication that Tarceva can slow disease progression" to the extent implied by the hourglass presentation, nor do the pivotal trials demonstrate "a quality of life benefit for these patients."

OPDP also pointed to a presentation in the NSCLC visual aid where, in conjunction with the claim "[s]ignificantly increased disease control rate in a broad patient population," the visual aid included a graph that showed 35.1% stable disease in the Tarceva arm versus 26.5% in the placebo arm. Because neither stable disease nor disease control rate were pre-specified endpoints in Tarceva's pivotal study, OPDP concluded that the presentation misleadingly suggested a clinical benefit.

Minimization of Risk: OPDP concluded that the overall presentation in the visual aids minimized the risks associated with Tarceva. For example, important risk information was listed underneath

[3] Emphasis in original.

efficacy signals such as "Extending survival for moments that matter." Additionally, the back page of the pancreatic cancer visual aid summarized key promotional messages about Tarceva, but "fail[ed] to mention any of the serious, potentially fatal risks associated with Tarceva."

CellTex Warning Letter

Promotion of Unapproved Use: OCBQ issued a warning letter to CellTex on September 24, 2012 alleging, among other things, that CellTex was improperly marketing its adipose derived mesenchymal stem cell (AdMSC) product without an approved biologics license application (BLA) as required by the Public Health Service Act (PHSA). In a heavily redacted letter, OCBQ also claimed that Celltex was engaging in improper promotion. The agency noted that CellTex promoted its unapproved AdMSC product and process to physicians "by encouraging physicians to enroll patients in one of [CellTex's] clinical trials." OCBQ pointed to CellTex's protocols, which hypothesized that patients enrolled in these clinical trials could clinically benefit from the AdMSC product. Because CellTex did not have an approved BLA, and because there was no investigational new drug application in effect, OCBQ concluded that the AdMSC product violated the Federal Food, Drug, and Cosmetic Act and the PHSA.

Acu-International Warning Letter

Lack of Necessary Clearance: The CDRH Office of Compliance reviewed a website for Acu-International's Electro Meridian Imaging (EMI) device (http://www.emi4.com/). The website stated that the EMI device "is used with acupuncture needles and 'measures the 24 meridian points on your body' to help diagnose and treat patients." CDRH explained that acupuncture needles are Class II devices, which require the submission and clearance of a premarket notification, commonly known as a 510(k). Because CDRH concluded that the EMI device is an accessory to a Class II device, the EMI device also required 510(k) clearance. CDRH stated that the website's claims rendered the EMI device adulterated and misbranded because Acu-International's website was advertising the EMI device without marketing clearance or approval.

PC Tan Warning Letter

Lack of Necessary Clearance: CDRH reviewed a PC Tan website (http://www.pctan.com/equipment.php) and found claims relating to three KBL brand devices: the Mon Amie, Optima, and pureCollagen. The claims stated:

- "mon amie . . . •Tanning & Red Light Lamp Combination"
- "Optima . . . •Tanning & Red Light Lamp Combination"
- "pureCollagen . . . There are 3 different programs: body forming, health training or target muscle formation."

CDRH found that the addition of the red LED light constituted a new tanning device technology. Although UV tanning beds are exempt from the requirement to submit a premarket notification when they use only UV light bulbs, "[o]nce additional wavelengths are added, in this case the red light bulbs, the tanning bed is no longer exempt and would require a premarket submission." Further, CDRH found that the pureCollagen device had not been proven safe and effective for the advertised uses. CDRH concluded that all three devices were adulterated and misbranded.

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