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E-ALERT | Food & Drug

May 30, 2013

SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

APRIL 2013

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, medical devices, and biologics.

In April 2013, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letter on FDA's website:[1]

- Untitled letter to Teva Neuroscience, Inc. re: ANDA 076809 Clozapine tablets USP MA #44 (April 8, 2013) ("Teva Untitled Letter")

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

- Warning Letter to Medicamat S.A. (April 19, 2013) ("Medicamat Letter")

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:

- Untitled letter to RegenLab America Inc. re: RegenKit®-THT BK090048 (April 19, 2013) ("RegenLab Untitled Letter")

This alert merely summarizes the allegations contained in FDA's letters. It 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.

LETTER ISSUED BY OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

Teva Untitled Letter

Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. OPDP reviewed an article detailer for clozapine, produced by Teva, and alleged that the article detailer is misleading because it makes unsubstantiated superiority claims and omits and minimizes risk information.

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[1] Only enforcement letters posted to FDA's website in April 2013 are included herein. Letters issued in April but not posted to the website by April 30, 2013 will be summarized in our alerts for the months in which those letters are posted.

Unsubstantiated Claims / Unsubstantiated Superiority Claim: The article detailer included, among other things, the following statements about the effectiveness of three different drugs (including cozapine) on five symptom "clusters" associated with schizophrenia:

- "Treatment with the three atypical agents studied (clozapine, olanzapine, and risperidone) was associated with significant improvements in 3 of 5 PANSS symptom clusters (positive, cognitive, depression/anxiety). Clozapine and olanzapine showed improvement in the negative cluster.

  Only clozapine was associated with significant improvement in the excitement symptom cluster."[2]
- "Both clozapine and olanzapine improved the *negative* symptom cluster in a similar manner."[3]
- "Clozapine, olanzapine, and risperidone all significantly improved the *positive, cognitive*, and *depression/anxiety* symptom clusters."[4]
- "**The excitement domain findings of this study 'further point to clozapine's efficacy for patients having difficulty with aggression and impulse control.'**"[5]

OPDP alleged that these claims are misleading because they "imply that clozapine demonstrated significant efficacy in treating four of the five 'symptom clusters' associated with schizophrenia … when this has not been demonstrated by substantial evidence or substantial clinical experience." FDA noted that the claims were based on a retrospective, Positive and Negative Syndrome Scale ("PANSS") derived five-factor analysis of data from a previously published prospective, randomized, 14-week clinical trial. FDA stated that this type of retrospective analysis does not constitute substantial evidence or substantial clinical experience and thus cannot be used to support the claims.

Furthermore, OPDP stated that the claims "Clozapine was superior to both risperidone and haloperidol in treating the *excitement* cluster" and "[o]nly clozapine was associated **with improvement in the excitement domain,**"[6] in conjunction with the comparative graphic presentation detailing the results of the PANSS-derived five factor analysis, misleadingly suggest that clozapine is superior to the other drugs studied in the excitement symptom cluster. OPDP noted that a single retrospective analysis is not considered substantial evidence or substantial clinical experience to support the "implication" of superiority for clozapine. Instead, OPDP stated that a head-to-head study is required.

Omission and Minimization of Risk Information: OPDP also stated that the article detailer failed to disclose (1) that clozapine is contraindicated in patients with hypersensitivity to clozapine or any other component of the drug; and (2) numerous risks associated with clozapine such as QT interval prolongation, fever, and hepatitis (among others). OPDP noted that while the article detailer included limited information regarding QT interval prolongation, it failed to mention that clozapine treatment should be discontinued if the QTc interval exceeds 500 milliseconds, as stated in the approved label.

OPDP also alleged that the article detailer misleadingly presented numerous efficacy claims by using colorful pictures, graphics, and large bolded headers surrounded by white space, while providing risk information in smaller print and in block paragraph format on the back page. Although, OPDP noted that the article detailer included the bolded statement "**Please see back cover for additional**

[2] Emphasis in article detailer.
[3] Emphasis in article detailer.
[4] Emphasis in article detailer.
[5] Emphasis in article detailer.
[6] Emphasis in article detailer.

indications, Important Safety Information, and enclosed Prescribing Information, including Boxed Warnings" on the bottom of page three (out of four). In OPDP's view, however, this did not mitigate the misleading risk presentation.

LETTER ISSUED BY CDRH OFFICE OF COMPLIANCE (OC)

Medicamat Warning Letter

Medicamat's "Punch-Hair-Matic-S.A.F.E.R." device is registered and listed as a Class I device, under an exemption for manual surgical instruments for general use (21 C.F.R. 8278.4800). According to CDRH's warning letter to Medicamat, Medicamat's "Punch-Hair-Matic-S.A.F.E.R." device is misbranded because it is improperly registered as an exempt Class I device. CDRH stated that devices classified under this provision are intended to automate hair transplant for the surgical treatment of baldness, but Medicamat's device is indicated to treat the first stages of male and female diffuse hair loss and for thickening of the glabrous skin and eyebrow repair. According to CDRH, Medicamat's device thus exceeds the limitations of 21 C.F.R. 878.9(a) because it has a different intended use than devices classified under 21 C.F.R. 878.4800, and is thus not exempt from premarket notification.

LETTER ISSUED BY CBER OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY (OCBQ)

RegenLab Untitled Letter

The RegenKit-THT was cleared for marketing under premarket notification (510(k)) submission, which included the following Indications for Use statement:

> The RegenKit®-THT is designed to be used for the safe and rapid preparation of autologous plateletrich plasma (PRP) from a small sample of blood at the patient's point of care. The PRP is mixed with autograft and/or allograft bone prior to application to an orthopaedic surgical site as deemed necessary by the clinical use requirements.

OCBQ alleged that RegenLab's website, a tri-fold patient brochure, and a professional brochure provide evidence that RegenLab is marketing its RegenKit-THT for cosmetic uses. OCBQ noted that the marketing materials contain "before" and "after" pictures of patients whose skin supposedly benefited from the use of RegenKit-THT. In addition, OCBQ cited the following statements:

- "Deemed in the media as the "Vampire Lift", people everywhere are learning that their own stem cell growth factors are the underlying drivers of having sustainable healthy skin. CALL NOW to ask your Eclipse Representative how unleashing the simple, quick, and advantageous RegenLab process into your practice will strengthen your aesthetic treatment outcomes and your profit margin!"
- "Order a RegenLab™ Starter Pack and receive a FREE centrifuge and marketing kit!…[a]verage duration of a full-face treatment is 30-40 minutes."
- "With a simple, quick[,] and advantageous RegenLab™ process, your own blood is safely prepared on the physician's premises and is delivered to your skin within the same treatment session."
- "RegenPlasma™ is regenerative medicine and works best aesthetically when it is introduced into the skin."

- "[A]ccording to studies, the main goal of a RegenPlasma™ treatment is to stimulate fiberblast [sic] and develop long-term collagen formations in the dermis."
- "Most patients enjoy quantifiable improvements in skin complexion, texture[,] and tone usually within three weeks."

OCBQ's letter alleged that these claims for cosmetic uses establish a new intended use for the device. Because the company lacks a clearance or approval for such intended uses, OCBQ alleged that these claims misbranded and adulterated the device.

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