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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

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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 February 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letter on its website:[1]

- Untitled letter to Novartis Oncology re: Gleevec® (imatinib mesylate) tablets for oral use (January 9, 2012) ("Novartis Oncology Untitled Letter")[2]

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

- Warning letter to BioElectronics Corporation re: ActiPatch, RecoveryRx, and Allay (January 31, 2012) ("BioElectronics Warning Letter")

During February 2012, the Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) did not post any enforcement letters relating to the advertising and promotion of biologics on FDA's website. The letters posted by OPDP and CDRH 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. 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.

Overstatement of Efficacy

FDA's letters contain the following allegations under an "Overstatement of Efficacy" subheading:

Novartis Oncology Untitled Letter: Gleevec is indicated for, among other things, patients with Kit (DC117) positive [KIT+] unresectable and/or metastatic malignant gastrointestinal stromal tumors [GIST]. Novartis Oncology submitted three "GISTexchange Case Highlight[s]" (GLI-1006264, GLI-1006367, GLI-1006265) under cover of Form FDA 2253. In part, the promotional case studies claimed:

[1] Only enforcement letters posted to FDA's website in February 2012 are included herein. Letters issued in February but not posted to the website by February 29, 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.

- "Following 5 years of Gleevec therapy, disease progression was observed . . . ."
- "Six months after starting Gleevec therapy, a [computed tomography] CT scan revealed a decrease in the size of the hepatic metastases. . . . Subsequent CT monitoring over several years showed stable disease. After 5 years on Gleevec at 400 mg/d, a restaging CT revealed progressive disease . . . ."
- "The patient has been on Gleevec for over 3.5 years, and remains free of disease and any supervening medical problems."

According to OPDP, these claims misleadingly implied that all patients with Gleevec achieved these results, despite the fact that the data in support of the claims came from a single patient. According to FDA, "[a] selected case study of one patient's treatment response does not constitute substantial evidence." Specifically, OPDP reasoned that the five-year progression free survival (PFS) claimed in the Case Highlight was significantly longer than the median PFS observed in clinical trials, where patients receiving Gleevec 400 mg/day experienced a median PFS of 18.9 months. As for the third claim, none of the pivotal clinical trials used disease free survival as a predefined endpoint, and OPDP found that there is no substantial evidence or substantial clinical experience that demonstrates Gleevec is effective in controlling other supervening medical problems. Although the Case Highlights included disclaimers stating that "results are not necessarily representative and may vary by patient," FDA determined that these disclaimers did not mitigate the misleading nature of the claims and presentations.

Additionally, OPDP found that the following claims overstated the efficacy of Gleevec therapy:

- "Progressive disease may occur in about 13% of patients with unresectable or metastatic GIST treated with Gleevec 400 mg/d."
- "A randomized, phase 3 study reported that **approximately 1 in 3 patients** who had progressive disease while being treated with Gleevec 400 mg/d **benefited** from dose escalation to 800 mg/d."[3]
- "Follow-up MRIs with and without contrast were performed 2 years after the initial diagnosis and showed that the abdomen and pelvis were completely unremarkable . . . ."

OPDP concluded that the findings from the clinical trials of Gleevec did not support these claims. First, analysis of the pivotal clinical studies showed that 75%—not 13%—of the patients with unresectable or metastatic GIST treated with Gleevec 400 mg/day progressed during the study. Second, in claiming that dose escalation resulted in a benefit to approximately 1 in 3 patients who had progressive disease, Novartis Oncology combined the percentage of patients who achieved a partial response (2.3%) and the percentage of patients who had stable disease (27.1%). Because stable disease is not considered to be an accurate indicator of therapeutic effect due to drug therapy in patients with GIST, however, this claim misleadingly implied efficacy benefits of Gleevec therapy that had not been demonstrated by substantial evidence or substantial clinical experience. Similarly, with respect to the claim that complete response (CR) to therapy (i.e., the disappearance of all target lesions) lasts for at least two years, a phase two study presented on Gleevec's PI states that the single CR reported in the study lasted 11 months. Only when the CR and partial responses (PR) were combined did the estimated median duration increase to 118 weeks. Thus, the claim that complete response duration lasted two years was not supported by the data, and the claim misleadingly implied that this observation in a single patient was representative of the typical response that patients may expect from Gleevec.

[3] Emphasis added by OPDP.

Unsubstantiated Efficacy Claims

FDA's letters contain the following allegations under an "Unsubstantiated Efficacy Claims" subheading:

Novartis Oncology Untitled Letter: The Case Highlight titled "A Patient with Unresectable KIT + GIST" made the following claim: "Gleevec 400 mg/d was given for 3 months. Following treatment, the patient's melana resolved and hemoglobin remained between 9.5 and 10.0 g/dL." According to OPDP, this claim misleadingly implied that Gleevec is effective at treating melana, when neither substantial evidence nor substantial clinical experience had demonstrated Gleevec's ability to improve disease-related symptoms, such as melana.

Claims Outside Cleared Use[4]

FDA's letters contain the following allegations under a "Claims Outside Cleared Use" subheading:

BioElectronics Warning Letter: FDA has cleared BioElectronics' ActiBand device "for the treatment of edema following Blepharoplasty." CDRH reviewed several of BioElectronics' websites[5] and found numerous claims related to BioElectronics' ActiPatch, RecoveryRx, and Allay devices that FDA considered to be outside the indication for use of the ActiBand device. Specifically, CDRH pointed to claims such as:

- "ActiPatch works to relieve your heel pain . . . ."
- "ActiPatch . . . Pain in your elbow? Gone."
- "RecoveryRx . . . Reduces Swelling, Bruising, & Pain."
- "RecoveryRx . . . Accelerates The Natural Healing Process."
- "Allay . . . Menstrual Pain Therapy."
- "Allay . . . quickly relieve edema, inflammation, and pain . . . ."

CDRH concluded that these claims, among others, represented major changes or modifications in the cleared intended use of the ActiBand device. Furthermore, BioElectronics had not obtained marketing authorization before offering ActiPatch, RecoveryRx, or Allay devices for sale, rendering the devices adulterated under section 501(f)(1)(B) of the Federal Food, Drug, and Cosmetic Act. CDRH requested that BioElectronics immediately cease the dissemination of promotional materials for ActiPatch, RecoveryRx, and Allay that bear these or similar claims, and reminded BioElectronics that it was not permitted to market a device for any intended use outside of the company's 510(k) clearance unless it first obtained appropriate marketing authorization.[6]

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[4] The letter issued by CDRH does not explicitly use this subheading, but the allegations fit within this category.
[5] CDRH reviewed the following websites: www.actipatchstore.com, www.allaystore.com, www.actipatch.ca, and www.bielcorp.com.
[6] Additionally, CDRH determined that, had they been cleared, the ActiPatch and Allay devices would have been misbranded because their labels failed to include cautionary statements restricting sale of the devices by or on the order of a practitioner.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug practice group:

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