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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

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

- Untitled letter to Eli Lilly and Company re: Amyvid™ (Florbetapir F 18 Injection) for intravenous use (August 10, 2012) ("Eli Lilly Untitled Letter")[2]
- Warning letter to Jazz Pharmaceuticals re: FazaClo® (clozapine, USP) Orally Disintegrating Tablets (September 18, 2012) ("Jazz Warning Letter")
- Untitled letter to Endo Pharmaceuticals Inc. re: VANTAS® (histrelin acetate) subcutaneous implant (September 25, 2012) ("Endo Untitled Letter")

During September 2012, the Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) and 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 or devices, respectively, on FDA's website. The letters posted by OPDP raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded.

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.

Eli Lilly Untitled Letter

According to its prescribing information (PI), Amyvid is indicated for "Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline." OPDP concluded that a multi-colored image of the brain presented on Eli Lilly's webpage, and at an annual meeting of the American Academy of Neurology, was misleading and misbranded Amyvid.

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[1] Only enforcement letters posted to FDA's website in September 2012 are included herein. Letters issued in September but not posted to the website by September 30, 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.

Misleading Presentation: In addition to the risk of radiation exposure, Amyvid's PI contains Warnings and Precautions on the risk of image misinterpretation. The PI provides that Amyvid PET scans should be displayed and interpreted using a black-and-white scale, and includes several examples of such scans to show proper interpretation. Further, Amyvid's PI does not include instructions for evaluating β-amyloid neuritic plaque density using a color scale. The brain image featured on Eli Lilly's webpage and at the AAN annual meeting was multi-colored. Due to the precautions in the PI on the risk of image misinterpretation, OPDP concluded that Eli Lilly's use of a color PET scan brain image was misleading and misbranded Amyvid. According to the untitled letter, Eli Lilly provided a written commitment on June 5, 2012 to immediately cease dissemination of these materials.

Jazz Warning Letter

FazaClo is indicated for "the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia." Additionally, FazaClo is indicated for "reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior[.]" According to its PI, FazaClo should be used only in patients experiencing treatment-resistant schizophrenia, due to the significant risk of agranulocytosis (acute, severe leukopenia) and seizure associated with the use of FazaClo. OPDP found that a direct-to-consumer brochure misbranded FazaClo because it omitted and minimized important risk information, broadened the approved indication, presented unsubstantiated superiority claims, and overstated the drug's efficacy.

Omission and Minimization of Risk Information: OPDP found that, in addition to omitting all contraindications and common adverse reactions, the brochure failed to disclose material information regarding the warnings listed in FazaClo's PI. Specifically, although the brochure disclosed the risk of agranulocytosis associated with the drug, it omitted "the important material fact that agranulocytosis is a **potentially life-threatening** adverse reaction."[3] Similarly, although the brochure directed patients to see the full PI regarding the risk of seizures, dementia-related psychosis in elderly patients, myocarditis, and other adverse cardiovascular and respiratory effects, it omitted material facts regarding each of these risks, including that:

- elderly patients with dementia-related psychosis treated with antipyschotic drugs are at an increased risk of death, and FazaClo is not approved for use in these patients;
- patients with predisposing factors, such as a history of seizures, should use FazaClo with caution; and
- patients should not engage in activity where a sudden loss of consciousness poses a serious risk to the patient or others.

Further, OPDP determined that the brochure prominently presented efficacy claims, but relegated the risk information to a brief description beginning on page 8 of the 12-page brochure. Even though page 3 directed patients to see the safety information listed later in the brochure, OPDP found that this did not mitigate the otherwise misleading presentation.

Broadening of Indication: OPDP concluded that the brochure contained claims that misleadingly implied FazaClo is indicated for the overall treatment of schizoaffective disorder. OPDP pointed to the claim:

> FazaClo is a medication prescribed to treat the symptoms of schizophrenia and schizoaffective disorders in patients who have not had good results with

[3] Emphasis added by OPDP.

other medications. FazaClo also reduces the risk of recurrent suicidal behavior in patients with these disorders.

Additionally, the brochure contained a section titled "**What is schizoaffective disorder?**"[4] that provided an overview of the symptoms patients with the disorder may experience. OPDP found that this claim and presentation suggested FazaClo is approved for the general treatment of schizoaffective disorder, when in fact it is only indicated for reducing the risk of recurrent suicidal behavior in patients with schizoaffective disorder, and only in "severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia."[5]

Unsubstantiated Superiority Claims: OPDP found that claims in the brochure misleadingly suggested that FazaClo is more effective than, or otherwise superior to, other schizophrenia treatments. For example, the brochure claimed as follows: "Researchers say that clozapine, the active ingredient in FazaClo, is the most effective medication for reducing or eliminating symptoms in patients who have not had success with other products." The brochure also claimed that "FazaClo generally produces little or none of the restlessness, stiffness, shakiness, or tremor you may have experienced with other medications." OPDP acknowledged that clozapine has been demonstrated to be more effective than chlorpromazine, and is the only product approved to manage treatment-resistant schizophrenia in severely ill patients. Nevertheless, FDA explained that it is unaware of adequate, well-controlled studies demonstrating clozapine's superiority to all other products.

Overstatement of Efficacy: OPDP found that several claims in the brochure misleadingly implied that FazaClo would improve specific individual symptoms—such as agitation, unusual thoughts, hearing voices, and impairment of academic, work, or social functioning—when there was not substantial evidence or substantial clinical experience to support such claims. FazaClo's clinical trial evaluated composite scale scores, including the Brief Psychiatric Rating Scale (BPRS)[6] and the Clinical Global Impression (CGI) scale. As OPDP explained, "[d]emonstrating an effect on the composite total scores of these scales does not demonstrate an effect on an individual component of these scales." Accordingly, OPDP found that the brochure's claims with respect to individual symptoms—such as "[o]ver a period of time, symptoms like voices or unusual thoughts usually diminish or disappear"—and claims with respect to unmeasured symptoms—such as "[y]ou may experience renewed interest in attending school, or holding a job"—were unsubstantiated.

Additionally, OPDP found that the claims misleadingly suggested that treatment with FazaClo would completely resolve the symptoms of patients with treatment-resistant schizophrenia. Specifically, the brochure explained that clozapine "eliminates" symptoms. It also stated that FazaClo will cause symptoms to "disappear," and that FazaClo is "**[a] new road to recovery**."[7] OPDP explained that the clinical trial results did not support claims of complete recovery or elimination of symptoms, and therefore these claims were unsubstantiated and misleading.

Endo Untitled Letter

Vantas is indicated for the palliative treatment of advanced prostate cancer. OPDP found that a Vantas caregiver brochure was misleading because it omitted serious risk information.

Omission of Risk Information: Endo's caregiver brochure made claims regarding Vantas' efficacy and dosing regimen. For example, the brochure claimed:

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[4] Emphasis in original.
[5] Emphasis added by OPDP.
[6] This score reflects a cluster of four key items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought criteria.
[7] Bolded emphasis in original, underlined emphasis added by OPDP.

> VANTAS® is one type of GnRH [gonadotropin releasing hormone] agonist that may help relieve the symptoms of prostate cancer; it is not a cure. It is implanted into the arm and is designed to continuously deliver drug every day for 12 months. Because of its once-yearly administration, VANTAS may mean fewer interruptions to your loved one's life, and possibly yours.

OPDP concluded that these claims misleadingly suggested Vantas is safer than has been demonstrated. Vantas' PI contains numerous warnings and precautions regarding the risk of spinal cord compression, ureteral obstruction, hyperglycemia, diabetes mellitus, myocardial infarction, sudden cardiac death, and stroke. The brochure, however, failed to include these risks. OPDP found that this omission was misleading, and that the brochure misbranded Vantas.

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