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FDA Advertising and Promotion Enforcement Activities: Update

November 20, 2018

Food, Drugs, and Devices

This e-alert is part of a series of e-alerts summarizing publicly available U.S. Food and Drug Administration (FDA) enforcement letters (i.e., warning letters and untitled letters) relating to the advertising and promotion of prescription drugs, medical devices, and biologics.

In October, the Office of Prescription Drug Promotion (OPDP) posted the following warning and untitled letters on FDA's website:

- Warning Letter to MannKind Corporation re: NDA 022472 AFREZZA® (insulin human) inhalation powder, for oral inhalation use, MA 439 (Oct. 5, 2018) ("Afrezza Warning Letter")
- Untitled Letter to Eisai Inc. re: NDA 202834 Fycompa® (perampanel) tablets, for oral use, CIII, and NDA 208277 Fycompa ® (perampanel) oral suspension, CIII MA 352 and MA 78 (Oct. 11, 2018) ("Fycompa Untitled Letter")
- Warning Letter to Vanda Pharmaceuticals Inc. re: NDA 022192 FANAPT® (iloperidone) tablets, for oral use MA 539 and NDA 205677 HETLIOZ® (tasimelteon) capsules, for oral use MA 137 (Oct. 22, 2018) ("Fanapt/Hetlioz Warning Letter")

The OPDP letters are the fifth, sixth, and seventh enforcement letters OPDP has issued in 2018, and the first two warning letters OPDP has issued this year. FDA's Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality (OCBQ) and Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) did not post any enforcement letters relating to advertising and promotion on FDA's website in September or October.

This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analyses, 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.

Office of Prescription Drug Promotion (OPDP)

Afrezza Warning Letter (October 2018)

OPDP states that MannKind's Facebook post ("post") misbrands Afrezza because it makes false or misleading claims and/or representations about the risks associated with Afrezza by

suggesting that there are no safety concerns associated with use of the drug. These allegations were submitted to OPDP as part of the office's Bad Ad Program.

False or Misleading Risk Presentation

OPDP alleges that the post misbrands Afrezza by suggesting that there are no risks associated with the use of the drug. Specifically, the post includes the following claims and presentations (emphasis in original):

- **"Afrezza Inhalation Powder"** . . .
- "Insulin is not the bad guy. If your doctor is advising you to start taking insulin it will help your body work its best and protect you from health complications."
- **"My body stopped making insulin. So I take insulin. No drama.**"

OPDP states that the post claims "Afrezza Inhalation Powder" "will help your body work its best and protect you from health complications" with "no drama," but that "this may not be the case."

Afrezza is indicated to improve glycemic control in adult patients with diabetes mellitus, and it has three limitations of use, including: (1) Afrezza is not a substitute for long-acting insulin and must be used in combination with a long-acting insulin in patients with type 1 diabetes mellitus; (2) Afrezza is not recommended for the treatment of diabetic ketoacidosis; and (3) the safety and efficacy of Afrezza in patients who smoke has not been established, and the use of Afrezza is not recommended in patients who smoke or who have recently stopped smoking. Furthermore, Afrezza carries a boxed warning for the risk of acute bronchospasm in patients with chronic lung disease, and it is contraindicated during episodes of hypoglycemia, in patients with chronic lung disease, and in patients with hypersensitivity to regular human insulin or any of the Afrezza excipients. Afrezza also carries other warnings and precautions.

OPDP states that by suggesting there are no risks associated with use of Afrezza, the post is misleading with respect to the drug's safety. OPDP also states that the misleading impression from the claims in the post is not mitigated by the statement, "Please see full Prescribing Information, including boxed WARNING, Medication Guide, and Instructions for Use" with a link to the prescribing information. Nor is the misleading impression mitigated by including some risk information regarding acute bronchospasm in a pop-up box that is visible when a cursor hovers over the thumbnail of the Afrezza logo in a corner of a post.

Fycompa Untitled Letter (October 2018)

OPDP states that oral statements made by an Eisai sales representative misbrand Fycompa by suggesting that the drug is intended for uses for which it lacked approval at the time, as well as for new uses for which it currently lacks approval, and for which its labeling did not and does not provide adequate directions for use. OPDP also alleges that the sales representative's statements are false and misleading because they minimize serious risks associated with use of the drug. These allegations were submitted to OPDP as part of the office's Bad Ad Program.

Lack of Adequate Directions for Use

OPDP alleges that the Eisai sales representative's statements, made during a lunch presentation, misbranded Fycompa by suggesting that the drug could be used for the treatment of partial-onset seizures ("POS") and primary generalized tonic-clonic ("PGTC") seizures in

patients as young as two years, and that pediatric data could be used for the treatment and dosing of POS and PGTC seizures in pediatric patients under two years. At the time the statements were made, however, Fycompa was approved only to treat POS or PGTC in patients 12 years or older. Specifically, the sales representative stated that Eisai had submitted a supplemental new drug application for the POS and PGTC seizure indications in patients as young as two years, and that the company should be getting FDA approval soon. The sales representative stated that the supplemental application was based on data extrapolated from adult studies and some pediatric studies.

OPDP acknowledged that on September 27, 2018, FDA approved Fycompa for the treatment of POS in patients four years or older, but stated that Fycompa remains unapproved for the treatment of POS in patients under four years and for the treatment of PGTC seizures in patients under 12 years. OPDP therefore concludes that the labeling for Fycompa does not provide adequate directions for use to treat POS in patients under four years, nor PGTC seizures in patients under 12 years, thereby rendering the drug misbranded. OPDP also states that the representative's statements suggesting that Fycompa is safe and effective for use in treating POS in patients under four years and PGTC seizures in patients under 12 years are misleading because Eisai has not provided data that supports such suggestions.

OPDP states that "[t]hese claims, which misleadingly suggest that Fycompa is safe and effective for uses for which it is not approved, are especially concerning from a public health perspective given the vulnerable pediatric patient population involved and the serious and life-threatening health risks associated with Fycompa." Fycompa contains a boxed warning regarding serious psychiatric and behavioral reactions, as well as warnings and precautions regarding suicidal behavior and ideation, neurologic effects, drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity, and withdrawal of antiepileptic drugs, and it is associated with other common adverse reactions.

OPDP further alleged "during the presentation, the sales representative minimized serious, life-threatening risks associated with Fycompa," including by downplaying risks of homicidal ideations and aggressive behavior and "by suggesting the healthcare practitioners should not worry about it." OPDP states that "[a]lthough the members of the audience asked for more information about the serious psychiatric and behavioral reactions . . .the representative further downplayed the risk . . . with anecdotal claims," and "noted that other epilepsy centers have this drug on formulary and were not concerned about the Boxed Warning." OPDP states that this misleadingly suggests that the drug is safer than has been demonstrated.

Fanapt/Hetlioz Warning Letter (October 2018)

OPDP alleges that Vanda's webpage titled, "Products" misbrands Fanapt and Hetlioz by being false or misleading because it presents information about the benefits of Fanapt and Hetlioz, but fails to include any risk information about either drug.

False or Misleading Risk Presentation

OPDP states that the webpage misbrands Fanapt and Hetlioz because it includes claims and/or representations about the uses and/or benefits of the drugs, but it fails to communicate any risk information. The webpage states that Hetlioz is approved for the treatment of Non-24-Hour Sleep-Wake Disorder, and Fanapt is approved for the treatment of schizophrenia in adults. The webpage also includes the statements, "For U.S. full prescribing information, including box

warnings and safety information, please visit www.fanapt.com," and "Full HETLIOZ® Prescribing Information can be found at: www.hetlioz.com." FDA acknowledges that the webpage includes the statements regarding full prescribing information, but states that such statements do not mitigate the omission of risk information from the webpage.

OPDP states that "[t]his misleading presentation is especially problematic from a public health perspective due to the serious and potentially life-threatening risks associated with the drugs, such as those contained in Fanapt's Boxed Warning." Fanapt carries a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis, and other warnings and precautions regarding cerebrovascular adverse reactions, QT prolongation, neuroleptic malignant syndrome, tardive dyskinesia, and others, as well as other common adverse reactions. Additionally, the approved indication for Fanapt includes language regarding the association of Fanapt with prolongation of the QTc interval, which has been associated in some other drugs with the ability to cause a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. Hetlioz also carries warnings and precautions regarding somnolence, and includes adverse reactions such as headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.

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