"A Perfect Storm": OPDP Sends Warning Letter Regarding Print Advertisement for Drug to Treat Opioid Use Disorder—Failure to Disclose Serious Risks, Including Potential for Fatal Overdose

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On December 2, 2019, the Food and Drug Administration's Office of Prescription Drug Promotion (OPDP) sent a Warning Letter to the sponsor of a drug that is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.[1] According to OPDP, the sponsor's print advertisement was false or misleading, because it omitted important risk information associated with the use of the drug. The print ad failed to disclose the potential for fatal overdose in this vulnerable patient population, and, as OPDP noted, opioid dependence and misuse is a significant public health concern and national crisis affecting millions of people.[2]

We will briefly describe OPDP's objections and note our observations. As we will explain below, a combination of factors likely contributed to a perfect storm, and the issuance of this Warning Letter.

Highlights

- The print ad contained claims about the benefits of the drug, but omitted information from the Warnings and Precautions section of the approved labeling (prescribing information or PI) concerning vulnerability to opioid overdose, a potentially fatal risk.
  - According to the PI, patients treated with the drug are likely to have reduced tolerance to opioids (i.e., patients may respond to lower doses of opioids than previously used). This can result in potentially life-threatening opioid intoxication. Cases of opioid overdose with fatal outcomes have been reported in patients at the end of a dosing interval, after missing a dose, or after discontinuing treatment. Attempts by patients to overcome the blockade effect of the drug may also lead to fatal overdose.
- The print ad omitted a second Warning and Precaution concerning the risk of injection site reactions. According to the PI, in some cases, injection site reactions may be very severe, requiring surgical intervention. The letter noted that this is one of the risks addressed by the Risk Evaluation and Mitigation Strategy (REMS) for the drug. In addition, the print ad failed to disclose the most common adverse reactions associated with the drug.
- OPDP noted that the print ad included the bolded statement, "For additional Important Safety Information, please see the Brief Summary of Prescribing Information on adjacent pages." However, as OPDP has stated in numerous letters, this statement and the inclusion of the brief summary did not mitigate the misleading omissions of material risk information from the main body of the print ad.
- Finally, under the "Prior Communications" section of the letter, OPDP referenced two prior instances in which FDA raised concerns about the communication of risks associated with this drug.
  - A March 2011 OPDP advisory letter providing comments to the sponsor on proposed promotional materials for the drug. OPDP's specific comments were redacted.
  - In October 2018, the Division of Anesthesia, Analgesia, and Addiction Products (review division) sent an information request to the sponsor asking them to "describe any efforts you have made to ensure that prescribers and patients are

1 The Warning Letter can be accessed at www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/alkermes-inc-597260-12022019.

2 Reports indicate that the sponsor contends the ad is no longer in distribution.

aware of the risk of overdose." The sponsor responded, in part, stating that they have "undertaken numerous efforts to ensure that prescribers and patients are aware of the risk of overdose," and that one such measure was the "[i]nclusion of the risk of opioid overdose within the text of promotional materials for healthcare professionals, caregivers, and consumers …"

AGG Observations

- It is unusual for OPDP to issue a Warning Letter for one print ad. However, it is likely that the following factors combined to elevate this to a Warning Letter: (1) omission of the risk of potentially fatal overdose, (2) the opioid crisis, (3) this is a REMS drug, (4) OPDP's prior advisory comments, and (5) the sponsor's response to the letter from the review division.
- This Warning Letter reminds us of the importance of including the most serious risk information in the body of the ad. The PI for this drug has 5 Contraindications, and the sponsor mentioned all 5 in the ad. The PI has 11 Warnings and Precautions, and the sponsor neglected to mention any of them. OPDP objected to the omission of the first two, vulnerability to opioid overdose and injection site reactions. The ad also failed to include any information from the Adverse Reaction section of the PI. At a minimum, the ad should have the most common adverse reactions.
- OPDP's decision to reference its' previous advisory comments is a reminder that it is generally advisable to either follow OPDP's advisory comments or to discuss outstanding issues with OPDP in an attempt to resolve any differences.
- OPDP's decision to reference the review division's information request and the sponsor's response emphasizes (1) the close working relationship that OPDP has with the various review divisions, and (2) before sponsors make statements to FDA regarding the state of their promotional materials, they should review their promotional materials in detail.
- It is also worth noting that even if a promotional piece may no longer be in use, as was the case here, OPDP reserves the right to take action.

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