DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

John F. Weet, PhD
Vice President, Regulatory Affairs and Quality Assurance
Collegium Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021

RE: NDA 208090
XTAMPZA ER™ (oxycodone) extended-release capsules, for oral use, CII
MA 114

Dear Dr. Weet:

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed an exhibit booth (PP-XT-US-0275) for XTAMPZA ER™ (oxycodone) extended-release capsules, for oral use, CII (Xtampza ER) submitted by Collegium Pharmaceutical, Inc.'s (Collegium) under cover of Form FDA 2253. The exhibit booth was displayed at the American Society Health-System Pharmacists (ASHP) Summer Meetings & Exhibition 2017 held in Minneapolis, Minnesota on June 3-7, 2017, and viewed by an OPDP representative. The exhibit booth makes false or misleading representations because it fails to adequately communicate information about the serious risks associated with Xtampza ER use. Therefore, the exhibit booth misbrands Xtampza ER within the meaning of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). *Cf.* 21 CFR 202.1(e)(3)(ii), (e)(5). These violations are particularly concerning given the serious public health impacts of opioid addiction, abuse, and misuse that can lead to overdose and death.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Xtampza ER.[1,]

> XTAMPZA ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Limitation of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve XTAMPZA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

XTAMPZA ER is not indicated as an as-needed (prn) analgesic.

The prescribing information (PI) for Xtampza ER contains boxed warnings regarding: addiction, abuse, misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; interactions with drugs affecting cytochrome P450 isoenzymes; and risk from concomitant use with benzodiazepines or other CNS depressants. According to the CONTRAINDICATIONS section of the PI, Xtampza ER is contraindicated in patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (e.g., anaphylaxis) to oxycodone. In addition the WARNINGS AND PRECAUTIONS section includes risk information regarding: life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients; adrenal insufficiency; severe hypotension; risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness; risks of use in patients with gastrointestinal conditions; risk of use in patients with seizure disorders; withdrawal; and risks of driving and operating machinery. The most common adverse reactions are nausea, headache, constipation, somnolence, pruritus, vomiting and dizziness.[2]

Prior Communications

OPDP notes that our advisory comments dated September 9, 2016, addressed draft Collegium presentations for Xtampza ER with certain similarities to the exhibit booth in this letter. In these advisory comments, OPDP recommended that Collegium revise proposed presentations so that they did not misrepresent the approved indication or omit important context; misrepresent or omit important risk information; or omit other material information. In particular, we cautioned Collegium about failing to present risk information for Xtampza ER with a prominence and readability reasonably comparable to the presentation of benefits. We are concerned that Collegium is promoting Xtampza ER in a manner that fails to adequately present the very serious risks of the drug, despite this direction from OPDP.

False or Misleading Risk and Benefit Presentations

Promotional materials misbrand a drug if they are false or misleading with respect to risk or benefits. The determination of whether promotional materials are misleading includes,

[2] Reference is made to the Xtampza ER prescribing information (PI) approved by the U.S. Food and Drug Administration (FDA) on December 16, 2016, the PI applicable to the materials viewed at the American Society of Health-System Pharmacists Summer Meetings & Exhibit 2017 in Minneapolis, Minnesota.

among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The exhibit booth presentation made representations and/or suggestions about Xtampza ER but failed to adequately provide material information about the drug's limitations of use and the serious and life-threatening consequences that may result from the use of the drug, thereby creating a misleading impression about the drug's safety.

Specifically, the exhibit booth presentation included a principal display panel that prominently presented benefit claims about the abuse-deterrent properties of Xtampza ER, but failed to include any information with respect to the drug's limitations of use, which state that due to the risks of addiction, abuse, misuse, overdose and death, Xtampza ER should only be used in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Nor did the principal display panel include any information with respect to the indication or serious and life-threatening risks such as those contained in the product's BOXED WARNING.

We note that the exhibit booth did have a side panel that included information from the INDICATIONS AND USAGE/LIMITATIONS OF USE, BOXED WARNING, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections of the FDA-approved product labeling. However, as observed by an OPDP representative at the 2017 ASHP Summer Meetings & Exhibition, the side panel was located several feet away from the principal display panel, and, unlike the principal display panel, which utilized a blue background and large font size, the side panel utilized a much smaller font size and plain white background, without any visual elements linking it to the principal display panel.

In addition, the principal display panel prominently presented the following benefit claims for Xtampza ER at the top of the panel (references omitted):

> With DETERx technology, Xtampza ER maintains its extended-release profile even under rigorous manipulation
>
> ● Cutting
> ● Crushing
> ● Grinding
> ● Chewing
> ● Dissolving in ingestible solvents
>
> …and offers the flexibility of multiple administration options

While these benefit claims regarding Xtampza ER's abuse-deterrent properties were prominently presented at eye level and easy to read, material information from the PI regarding the limitation of such properties in preventing abuse was presented at the bottom of the panel near the floor. In particular, the bottom of the principal display panel included the following: "However, abuse of Xtampza ER by injection and by nasal and oral routes of

administration is still possible." In addition to this information being displayed near the floor, with much less prominence than the abuse-deterrence benefit claims, an OPDP representative at the 2017 ASHP Summer Meetings & Exhibition also observed that it was obscured by a table and chair, such that the material information about the limitations of the abuse deterrent properties of the product was not visible to viewers as a practical matter.

Presenting material information in this manner is not sufficient to ensure that the claims about abuse deterrent properties are truthful and non-misleading. The current opioid abuse epidemic is a critical public health matter. Promotional materials describing abuse-deterrent properties should specify which routes of abuse deterrence have been established for a product and for specified routes of administration should adequately present, with sufficient prominence, additional information to explain that even where abuse-deterrent properties do exist, these properties only make abuse by such routes more difficult, not impossible. Furthermore, as stated in the Xtampza ER labeling, opioid drugs with abuse-deterrent properties still expose users to the risks of addiction, abuse, and misuse.

The exhibit booth presentation described above presents purported benefits of Xtampza ER but does not adequately present the serious and potentially life-threatening consequences that may result from use of the product — risks that must be adequately and prominently disclosed in promotional materials for opioid products such as Xtampza ER to ensure that they are not false or misleading.

Conclusion and Requested Action

For the reasons discussed above, the exhibit booth misbrands Xtampza ER within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). *Cf.* 21 CFR 202.1(e)(3)(ii), (e)(5).

OPDP requests that Collegium immediately cease violating the FD&C Act as discussed above. Please submit a written response to this letter on or before February 24, 2018, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Xtampza ER that contain statements such as those described above, and explaining your plan for discontinuing such violative promotion.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.** A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 114 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Xtampza ER comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Koung Lee, RPh, MSHS
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel Skariah, PharmD, RAC
Team Leader
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KOUNG U LEE
02/09/2018

SAMUEL M SKARIAH
02/09/2018