



Robert D. Tessarolo
President and Chief Executive Officer
Cipher Pharmaceuticals Inc.
C/O Willcox & Savage, P.C.
440 Monticello Avenue, Suite 2200
Norfolk, VA 23510

RE: NDA 022370
CONZIP[®] (tramadol hydrochloride) extended-release capsules for oral use, CIV¹
MA 12

WARNING LETTER

Dear Mr. Tessarolo:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the professional detail aid (CNZSA03201402) for CONZIP[®] (tramadol hydrochloride) extended-release Capsules for oral use, CIV (ConZip) submitted by Vertical Pharmaceuticals, LLC (Vertical) under cover of Form FDA 2253.² The detail aid is false or misleading because it omits important risk information associated with the use of ConZip and omits other material facts. Thus the detail aid misbrands ConZip within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). *C.f.* 21 CFR 202.1(e)(3)(ii); (e)(5). These violations are concerning from a public health perspective because they create a misleading impression about the safety and approved indication for ConZip.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of ConZip³.

CONZIP is an opioid agonist 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 Reference is made to the ConZip prescribing information (PI) approved by the U.S. Food and Drug Administration (FDA) on December 16, 2016, the PI applicable to the materials submitted.

² Vertical holds the exclusive license from Cipher to market, sell, and distribute ConZip in the US.

³ 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/long-acting opioid formulations, reserve CONZIP 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.

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

The PI for ConZip contains boxed warnings regarding: addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; interactions with drugs affecting cytochrome P450 isoenzymes; and risks from concomitant use with benzodiazepines or other CNS depressants. According to the CONTRAINDICATIONS section of the PI, ConZip 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; hypersensitivity to tramadol; and concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days. In addition the WARNINGS AND PRECAUTIONS section includes risk information regarding: serotonin syndrome risk; increased risk of seizures; suicide risk; adrenal insufficiency; life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients; 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; anaphylaxis and other hypersensitivity reactions; withdrawal; and risks of driving and operating machinery. The most common adverse reactions are nausea, constipation, dry mouth, somnolence, dizziness, and vomiting.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, 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 detail aid makes representations and/or suggestions about the efficacy of ConZip such as the following:

- ConZip® CIV – All Day Pain Relief
- ConZip® CIV Measures Up
- ConZip® is an opioid agonist indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

However, the detail aid fails to communicate **any** risk information about the product. By omitting the risks associated with ConZip, including serious and potentially fatal risks, the detail aid fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the drug's safety, a concern heightened by the serious public health impacts of opioid addiction, abuse and misuse.

Omission of Material Facts

In addition, the detail aid is misleading because it fails to provide material information regarding ConZip's full FDA-approved indication, including important limitations of use. Specifically, it omits the material information presented below in bold font from the INDICATIONS AND USAGE section of the ConZip PI (bold emphasis added):

CONZIP is an opioid agonist 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.**

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/long-acting opioid formulations, reserve CONZIP 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.**
- **CONZIP is not indicated as an as-needed (prn) analgesic.**

Conclusion and Requested Action

For the reasons discussed above, ConZip is misbranded under FD&C Act. 21 U.S.C. 352(a); 321(n); 331(a). *C.f.* 21 CFR 202.1(e)(3)(ii); (e)(5).

OPDP requests that Cipher immediately cease misbranding ConZip and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before September 8, 2017, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for ConZip that contain representations such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of ConZip. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the

violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

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 12 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 Warning 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 ConZip comply with each applicable requirement of the FD&C Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew Haffer, PharmD
Director
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

CC: Brian Markison
Chief Executive Officer
Vertical Pharmaceuticals, LLC
400 Crossing Blvd
Bridgewater, NJ 08807

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW S HAFFER
08/24/2017