



TRANSMITTED BY FACSIMILE

Ira Weisberg, President/CEO
Amherst Pharmaceuticals, LLC
15 Benedict Crescent
Basking Ridge, New Jersey 07920

Dr. Warren P. Lesser, DBA, MBA,
President/CEO
Magna Pharmaceuticals, Inc.
10801 Electron Drive, Suite 100
Louisville, Kentucky 40299

RE: NDA 022196
Zolpimist (zolpidem tartrate) Oral Spray (C-IV)
MA 9

WARNING LETTER

Dear Mr. Weisberg and Dr. Lesser:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a webpage titled, "Product Information" for Zolpimist (zolpidem tartrate) Oral Spray (C-IV) (Zolpimist) on the website for Amherst Pharmaceuticals, LLC (Amherst).¹ OPDP has also reviewed Magna Pharmaceuticals Inc.'s (Magna)² booth with exhibit panels for Zolpimist that appeared in the main exhibit hall at the SLEEP 2017 Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS).³ The webpage and exhibit panels make false or misleading claims and/or representations about the risks associated with and efficacy of Zolpimist. Thus, the webpage and the exhibit panels misbrand Zolpimist within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a); see 21 CFR 202.1(e)(5). In addition, these materials were not submitted at the time of initial dissemination or publication as required by 21 CFR 314.81(b)(3)(i). These violations are concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Zolpimist.

¹ Available at <http://amherstpharmaceuticals.com/product-information.shtml> (Last accessed November 13, 2017)

² In 2015, Amherst entered into an agreement with MAGNA Pharmaceuticals Inc. in which Magna has the exclusive rights to market and sell Zolpimist.

³ The SLEEP 2017 | APSS Annual Meeting took place from June 3rd to 7th, 2017.

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Background

Below are the indication and summary of the most serious and most common risks associated with the use of Zolpimist.⁴ According to the FDA-approved product labeling (PI):

Zolpimist (zolpidem tartrate) Oral Spray (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

Zolpimist is contraindicated in patients with a known hypersensitivity to zolpidem. The PI contains warnings and precautions regarding central nervous system (CNS) depressant effects and next-day impairment, the need to evaluate for co-morbid diagnoses, severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavioral changes, use in patients with depression, respiratory depression, and withdrawal effects. The most commonly observed adverse reactions were drowsiness, dizziness, diarrhea, and “drugged feelings.”

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 webpage and the exhibit panels include claims and/or representations about the efficacy of Zolpimist. Both the webpage and the exhibit panels, however, fail to communicate **any** risk information. By omitting the risks associated with Zolpimist, the webpage and the exhibit panels fail to provide material information about the consequences that may result from the use of the drug and create a misleading impression about the drug’s safety. This misleading presentation is especially problematic from a public health perspective given the serious and potentially life-threatening risks associated with the drug.

False or Misleading Claims about Efficacy

Promotional materials misbrand a drug if they are false or misleading with respect to efficacy. 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.

⁴ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotion pieces cited in this letter.

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The webpage includes the following claims (emphasis added):

- “Zolpimist® (zolpidem tartrate) is a patented, FDA approved bioequivalent version of the market leading sleep aid, Ambien® in an oral spray formulation.”
- “Zolpimist® is engineered to outperform the oral tablets”
- “Using a proprietary and patented technology we deliver the drug as a fine mist into the mucosal membranes lining the cheeks in the mouth (buccal delivery). This mode of delivery offers some very clear advantages as compared to other delivery methods:
- Fast onset of action; Zolpimist® induces sleep three times faster than oral tablets – 10 minutes as compared to 30 – 40 minutes for oral tablets.
- No food effect that mitigates the efficacy of other zolpidem products”

The exhibit panels include the following claim (emphasis added):

- “Zolpimist Oral Spray works so fast, patients only take when needed and may avoid nightly tablet-formulation dependency!”

These claims misleadingly suggest that Zolpimist is clinically superior in efficacy to other oral zolpidem products in the treatment of insomnia because of its formulation and mode of delivery. The suggestions that Zolpimist will “outperform” or induce sleep three times faster than zolpidem oral tablets, or that patients treated with Zolpimist require less frequent treatment compared to those on the tablet formulation (i.e., “avoid nightly tablet-formulation dependency”), are misleading. No references are cited to support these claims of superior efficacy. In fact, Zolpimist was approved as a 505(b)(2) application and, as correctly noted in the first claim on the webpage, demonstrated bioequivalence to Ambien, a zolpidem oral tablet, in healthy young volunteers. FDA is not aware of data to support the claims that Zolpimist is clinically superior in efficacy to other oral zolpidem products or that patients treated with Zolpimist require less frequent treatment compared to those on the tablet formulation. If you have data to support these claims, please submit to FDA for review.

In addition, the claim that Zolpimist “induces sleep” in 10 minutes misleadingly suggests that the established therapeutic onset of action (i.e., time it takes patients to fall asleep) of Zolpimist is 10 minutes. Again, no references are cited to support this claim. FDA is also not aware of data to support this claim. If you have data to support this claim, please submit them to FDA for review.

Furthermore, the claim that with Zolpimist there is “[n]o food effect that mitigates the efficacy of other zolpidem products” is false or misleading. To the contrary, the DOSAGE AND ADMINISTRATION section of the PI states that, “[t]he effect of Zolpimist . . . may be slowed by ingestion with or immediately after a meal.” Additionally, according to the CLINICAL PHARMACOLOGY section of the Zolpimist PI, the results of a food-effect crossover study

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suggest that, “as with all zolpidem products, Zolpimist . . . should not be administered with or immediately after a meal.” Therefore, the claim that food does not have an effect on Zolpimist is false or misleading.

The webpage and exhibit panels make the following representations about the use of Zolpimist (emphasis added):

- “Zolpimist® (zolpidem tartrate) is a patented, FDA approved bioequivalent version of the market leading sleep aid, Ambien®”
- “Zolpidem is the most commonly prescribed agent for the treatment of insomnia”
- “Zolpimist is well absorbed and may facilitate all-night sleep.”

These presentations are misleading because the webpage and the exhibit panels fail to include material information regarding the FDA-approved indication for Zolpimist. Specifically, the webpage and the exhibit panels omit the following material information from the INDICATIONS AND USAGE section of the PI (emphasis added):

Zolpimist (zolpidem tartrate) Oral Spray (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

Failure to Submit Under Form FDA-2253

FDA regulations require any labeling or advertising devised for promotion of the drug product to be submitted at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product’s current professional labeling. A copy of the webpage and the exhibit panels were not submitted to OPDP under cover of Form FDA-2253 at the time of initial dissemination as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the webpage and the exhibit panels misbrand Zolpimist within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a); see 21 CFR 202.1(e)(5). Furthermore, Amherst and Magna did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Amherst and Magna immediately cease misbranding Zolpimist and/or cease introducing the misbranded drug into interstate commerce. Please submit a written

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response to this letter on or before November 29, 2017, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Zolpimist that contain statements such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Zolpimist. 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 9 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 Zolpimist complies 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 S.T. Haffer, Pharm.D.
Division Director
Division of Advertising and Promotion Review 1
Office of Prescription Drug Promotion

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
11/14/2017