Case Study

ZOLPIMIST

(zolpidem tartrate) Oral Spray (C-IV)

Bad Ad Case Study

Zolpimist (zolpidem tartrate) Oral Spray (C-IV)

Facilitator Guide

Approximate Time: 30 minutes

Exercise prerequisite:

Students should view the Bad Ad e-learning course located at www.fda.gov/BadAd prior to completing this exercise.

Student Materials:

Before the exercise:

- Zolpimist webpage
- Prescribing Information (PI) for Zolpimist

After the exercise:

- FDA Warning Letter for Zolpimist

Facilitator Materials:

- Facilitator guide (includes a detailed answer key for the case study)

Facilitator instructions:

1. Distribute the Zolpimist webpage along with the PI for Zolpimist. Please note that this exercise will only address the Zolpimist webpage and not the exhibit panels that are cited in the FDA Warning Letter. However, both the webpage and exhibit panels had similar issues.
2. Present the Background and Case Study Instructions shown below.
3. Allow students approximately 10 minutes to review the Zolpimist webpage.
4. Use the discussion questions in this guide to assist students in identifying prescription drug promotion issues of concern, including false or misleading statements.
5. After discussing the issues of concern, distribute the FDA Warning Letter for Zolpimist.

Background and Case Study Instructions[1]:

This promotional piece is a webpage for Zolpimist. Below are the indication and summary of the most serious and most common risks associated with the use of Zolpimist. According to the PI:

> Zolpimist 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 zolpidem in an oral spray formulation and is bioequivalent to AMBIEN® (zolpidem tartrate) tablets, for oral use. It is a controlled substance C-IV.

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."

Using the PI as a reference, identify the issues of concern in the webpage. (Approximately 10 minutes)

Discussion Questions:

General

1. What are the key promotional messages for Zolpimist on the webpage?

2. Based on your knowledge and information from the PI, which claims, if any, do you think are false or misleading?

Specific

1. Does the webpage adequately communicate adverse events and other risks associated with Zolpimist?

   (See Detailed Answer Key #1 – False or Misleading Risk Presentation)

[1] When FDA reviews a promotional piece, it determines whether the relevant legal and regulatory requirements are met, including whether the piece is truthful and not misleading, in light of the information available at that time.

2. Is there evidence to support the following claims on the webpage (emphasis added)?

    - "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"

    (See Detailed Answer Key #2 – False or Misleading Claims about Efficacy)

3. Is there evidence to support the following claim on the webpage?

    - "No food effect that mitigates the efficacy of other zolpidem products"

    (See Detailed Answer Key #3 – False or Misleading Claims about Efficacy)

4. Do the following claims provide accurate and complete information about the FDA-approved indication (emphasis added)?

    - "Zolpimist® (zolpidem tartrate) is a patented, FDA approved bioequivalent version of the market leading sleep aid, Ambien® . . . ."
    - "Zolpidem is the mostly commonly prescribed agent for the treatment of insomnia . . . ."

    (See Detailed Answer Key #4 – False or Misleading Claims about Efficacy)

Detailed Answer Key

1. False or Misleading Risk Presentation

The webpage includes claims and/or representations about the efficacy of Zolpimist. However, the webpage fails to communicate any risk information. By omitting the risks associated with Zolpimist, the webpage 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. This misleading presentation is especially problematic from a public health perspective given the serious and potentially life-threatening risks associated with the drug.

2. False or Misleading Claims about Efficacy

The webpage includes the following claims (emphasis added):

- "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"

These claims misleadingly suggest that Zolpimist is clinically superior in efficacy to other oral zolpidem products because of its formulation and mode of delivery. No references are cited to support these claims and the FDA is not aware of evidence to support them. In fact, Zolpimist was approved as a 505(b)(2) product and demonstrated bioequivalence and not superior efficacy to Ambien, a zolpidem oral tablet, in healthy young volunteers.

3. False or Misleading Claims about Efficacy

The webpage includes the claim that there is "[n]o food effect that mitigates the efficacy of other zolpidem products." This claim 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 suggest that, "as with all zolpidem products, Zolpimist . . . should not be administered with or immediately after a meal."

4. False or Misleading Claims about Efficacy

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® . . . ."

- "Zolpidem is the mostly commonly prescribed agent for the treatment of insomnia . . . ."

These presentations are misleading because they fail to include material information regarding the FDA-approved indication for Zolpimist. Specifically, the webpage omits 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.

Discussion and Outcome

The FDA issued a Warning Letter for this Zolpimist webpage on November 14, 2017. As a result, the manufacturer for Zolpimist stopped using the webpage and distributed an "Important Correction of Drug Information" to correct the violative messages cited in the Warning Letter. In addition, the manufacturer for Zolpimist stopped using other promotional pieces for Zolpimist that contained similar claims and presentations.