

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OND/ODE I
Division of Neurology Products**

NDA/BLA #s:	22-196
Products:	Zolpimist
SPONSOR:	Novadel
FROM:	Russell Katz, M.D.
DATE:	12/19/08

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Zolpimist, the subject of this NDA, contains the active ingredient zolpidem tartrate (sedative-hypnotic) of the reference listed drug, Ambien, which has been shown to be effective for the treatment of adults with insomnia characterized by difficulty with sleep onset. Zolpimist is a metered dose oral spray and therefore represents a new dosage form and new route of zolpidem tartrate. The therapeutic use of sedative-hypnotic products is associated with sleep-driving and other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) with amnesia for the event, and severe allergic reactions. Consequently, class labeling changes pertaining to these risks were required for all drug products that are indicated for the treatment of insomnia, including the reference listed drug, Ambien. Zolpimist is bioequivalent to Ambien, and the Zolpimist label is based on the Ambien label, which includes the class labeling language pertaining to the above risks.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Zolpimist to ensure that the benefits of the drug outweigh the risks of complex sleep-related behaviors, such as sleep-driving and sleep-eating, and severe anaphylactic and anaphylactoid reactions in

patients who take sedative hypnotics. In reaching this determination, we considered the following:

- A. Zolpimist is approved for the treatment of adults with insomnia characterized by difficulty with sleep onset. In the United States, approximately 30-40% of the adult population complains of insomnia.¹ However, since there are several hypnotic agents that have been approved for the treatment of insomnia characterized by difficulty with sleep in the United States, a proportion of the above adults with insomnia are expected to use Zolpimist.
- B. Insomnia is the difficulty falling asleep or staying asleep despite having an adequate opportunity for sleep. Insomnia is the most common sleep complaint in the adults having significant consequences on quality of life, healthcare utilization, and subsequent psychiatric disorders.¹
- C. Zolpidem tartrate was approved for the treatment insomnia on 12/16/1992. The efficacy was demonstrated in two controlled trials of up to 5 weeks in duration in adult subjects with chronic insomnia.
- D. Zolpimist (zolpidem tartrate) is approved to be taken once daily immediately before bedtime. Since insomnia is a chronic disorder, patients with insomnia are expected to take Zolpimist on a chronic intermittent basis.
- E. A review of available postmarketing adverse event reports indicate that the therapeutic use of sedative-hypnotic products is associated with sleep-driving and other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) with amnesia for the event, and severe allergic reactions. In many of the cases of sleep-driving, sedative-hypnotics were being used in ways that are not in keeping with the prescribing information and may increase the risk for these events (e.g., at doses above the recommended doses or together with alcohol and/or other central nervous system depressants).
- F. Zolpidem tartrate is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zolpimist poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zolpimist. FDA has determined that Zolpimist is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, Zolpimist. FDA has also determined that Zolpimist is a product for which patient labeling could help prevent serious adverse events.

REMS memo new approval template 11/3/08

The element of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS. The REMS must include a timetable for assessments that shall be no less frequent than 18 months, 3 years and 7 years after the REMS is approved.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 14, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products

From: Claudia Karwoski, PharmD. Director (Acting)
Division of Risk Management

Jodi Duckhorn, MA, Team Leader
**Patient Labeling and Education
Division of Risk Management**

Subject: Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Zolpimist (zolpidem tartrate) Oral Spray

Application Type/Number: NDA 22-196

Submission Number: S-020

Applicant/sponsor: NovaDel Pharma, Inc

OSE RCM #: 2008-1190

1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes a Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require sponsors of approved drugs to develop and comply with REMS section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

In an email communication dated December 2, 2008 and subsequent discussion between Cathleen Michalowski, the Regulatory Project Manager, DNP, the FDA informed the sponsor that a REMS is necessary for Zolpimist (zolpidem tartrate) Oral Spray. The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

DRISK completed a separate review of the Zolpimist Medication Guide and Patient Instructions for USE on September 10, 2008.¹

2 MATERIAL REVIEWED

- Proposed Zolpimist (zolpidem tartrate) Oral Spray Risk Evaluation and Mitigation Strategy (REMS), submitted on December 5, 2008.

3 RESULTS OF REVIEW

The proposed REMS includes the following:

- GOAL: The goal of the REMS is to effectively communicate to health care providers, practitioners, pharmacies, and patients the risks involved with Zolpimist (zolpidem tartrate) Oral Spray (Zolpimist) and how to use Zolpimist safely and effectively by review of the information provided in Medication Guide and Patient Instructions for Use.
- REMS Components:
 - Medication Guide - the proposed REMS states that the sponsor will insert the Medication Guide and Patient Instructions for Use into each unit of use carton of Zolpimist (zolpidem tartrate) Oral Spray. The carton will be provided directly to the patient at the time the prescription is dispensed by the pharmacy and requires no repackaging by the pharmacy.
 - Timetable for Submission of Assessments - the sponsor proposes REMS assessments 18 months, 3 years, and 7 years after initial marketing approval of Zolpimist. The sponsor will submit the assessment with 60 days of the close of the assessment interval.

Reviewer Comments:

¹ Sharon Mills. DRISK Review of Patient Labeling (Medication Guide with appended Patient Instructions for USE), signed in EFS September 10, 2008.

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- *Because the REMS include only a Medication Guide for patients, any reference to communicating the risks to healthcare providers or other healthcare professionals should be removed from the goal.*
- *Although the Sponsor does not propose other REMS components such as Communication Plan they state that the MG and PIFU will be available on the website under the Communication Plan section of the REMS.*
- *The timetable should start from the time of approval of the REMS.*

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor's proposed REMS for Zolpimist (zolpidem tartrate) Oral Spray generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. However, we have the following comments and recommendations:

1. Even though the product will be packaged in unit of use, the sponsor must comply with 21 CFR 208.24(d), which requires a statement alerting pharmacists to dispense the MG with the product is on the carton and container.
2. Regarding the proposed REMS:
 - The goal should be revised to take out reference to healthcare providers and other healthcare professionals since the MG is directed to the patient.
 - Please see Appendix 1 for suggested revisions to the proposed REMS.
3. The sponsor should submit for review a detailed plan to evaluate the patients' understanding about the safe use of Zolpimist (zolpidem tartrate) Oral Spray at least 2 months before they plan to conduct the evaluation. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Zolpimist (zolpidem tartrate) Oral Spray. This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.
4. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of patients' understanding of the serious risks of Zolpimist (zolpidem tartrate) Oral Spray

Please let us know if you have any questions.

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/s/

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