

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

OTHER REVIEW(S)

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 25, 2008

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

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

Subject: Abuse potential assessment of Zolpimist (Zolpidem tartrate) Oral Spray,
Indication: Short-term treatment of insomnia characterized by
difficulties with sleep initiation.
Sponsor: NovaDel Pharma Inc.
Submission: NDA 22-196 is located in the EDR. The submission includes
a section entitled "Abuse Potential of Zolpimist (zolpidem tartrate) Oral
Spray. Expert Report" (entitled *Abuse Potential of Zolpimist Oral Spray
by Alternate Routes of Administration*, in Module 5, Section 5.3.3.1.1).
Labeling is under Module 1, Section 1.14.1.; S0014 (8-29-08 Amendment)

Background

CSS has brought to the Division's attention two concerns: (1) Possible abuse-potential issues related to the pharmacokinetics of the product and potential protocol violations noted by the Office of Compliance, and (2) The development of strategies to minimize the possible increase in abuse of Zolpimist.

Current zolpidem abuse data show the following:

- 1) Nonmedical zolpidem related emergency department mentions in the Drug Abuse Warning Network (DAWN) increased 35 percent from 2004 to 2006;
- 2) Zolpimist may provide a more convenient and appealing formulation for abuse because it offers the first oral concentrated (50 mg/mL), sweet and flavored solution of zolpidem tartrate available on the market. ZolpiMist delivers 5 mg of zolpidem tartrate per 100 µL: after initial priming (5 actuations), after which 60 metered actuations per bottle remain.

CSS requested the Sponsor (August 6, 2008) to propose strategies to minimize the potential abuse and misuse of the new formulation. In response to that request, the

Sponsor proposed intensified monitoring of post-marketing adverse events as part of a postmarketing pharmacovigilance program.¹

The proposed plan will include maintenance of all adverse events in a centralized safety database with expedited reporting of what will be termed "Events of Interest". Individual case safety reports (ICSRs) that include these events will be submitted to the Agency as expedited reports whether or not the case as a whole meets the regulatory requirements for 15-Day Alert reports. These Events of Interest will be based upon the following MedDRA preferred terms:²

- Drug administered at inappropriate site
- Drug administration error
- Incorrect dose administered
- Incorrect route of drug administration
- Wrong technique in drug usage process
- Intentional drug misuse
- Accidental exposure
- Accidental overdose
- Intentional overdose
- Multiple drug overdose
- Multiple drug overdose accidental
- Multiple drug overdose intentional
- Overdose
- Drug abuser
- Substance abuser
- Dependence
- Drug dependence
- Drug tolerance
- Drug tolerance decreased
- Drug tolerance increased

In addition to expedited reporting of the above Events of Interest, the Sponsor proposes to include a discussion in the quarterly periodic report based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" and will review data from the following databases: Drug Abuse Warning Network (DAWN), and the Toxic Exposure Surveillance System (TESS) report prepared by the American Association of Poison Control Centers (AAPCC), currently the National Poison Data System (NPDS). Events will be entered into the safety database for individual case reporting and aggregate analysis.

¹ EDR-NDA 22-196 (SN 0014), August 29, 2008.

² Based on current MSSO MedDRA Version 11.0. ©2008, Northrop Grumman Corporation

CONCLUSIONS AND RECOMMENDATIONS

- 1- CSS recognizes that the rate of onset of action, including Tmax of Zolpimist is equivalent to the one reported by the Sponsor for the currently marketed Ambien tablets. Thus, it is expected that both formulations would have the same time to peak of reinforcing effects and similar reinforcing properties. The Office of Compliance findings that relate to protocol violations in the conduct of biopharmaceutical studies do not appear to impact the pharmacokinetic values reported by the Sponsor.
- 2- CSS finds the Sponsor's proposed postmarketing strategies to be acceptable. However, it is the Office of Surveillance and Epidemiology that makes the final determination on the adequacy of the proposed postmarketing plan and that of the reporting frequency.

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/s/

Silvia Calderon
11/25/2008 11:09:37 AM
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Michael Klein
11/25/2008 11:42:34 AM
PHARMACOLOGIST

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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: September 10, 2008

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

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Subject: Review of Patient Labeling (Medication Guide with appended
Patient Instructions for Use)

Drug Name(s): ZolpiMist (zolpiem tartrate) Spray, Metered for Oral use

**Application
Type/Number:** N22-196

Applicant/sponsor: NovaDel Pharma Inc.

OSE RCM #: 2008-1190

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1 INTRODUCTION

NovaDel Pharma Inc., submitted an original 505 (b)(2) New Drug Application, NDA # 22-196, for ZolpiMist (zolpidem tartrate) Spray, Metered for Oral use, on November 20, 2007. ZolpiMist is a nonbenzodiazepine hypnotic of the imidazopyridine class, and is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. This 505 (b) (2) NDA is supported by reference to the approved reference listed drug, Ambien (zolpidem tartrate) Tablets, under NDA 19-908.

A Supplemental Labeling Request Letter was sent on December 4, 2006, to sponsors of sedative-hypnotic products with an insomnia indication, including Ambien (zolpidem tartrate) NDA 19-908, requesting Class labeling changes including development of a Medication Guide (MG) for the identified serious and significant public health concern of "sleep driving and other complex behaviors." The sponsor is required to follow the innovator's (Ambien) labeling.

The sponsor's proposed labeling included Patient Instructions for Use within the Professional Information. The sponsor submitted updated labeling on June 20, 2008. The submission contains proposed draft Professional Information, including a draft MG for ZolpiMist, and Patient Instructions for Use (PIFU).

This review is written in response to a request from the review division for review of the proposed MG and PIFU by the Patient Labeling and Education Team.

2 MATERIAL REVIEWED

- DRAFT ZolpiMist PI, submitted by the sponsor on June 20, 2008 and further revised by the review division on September 3, 2008.
- DRAFT ZolpiMist MG and PIFU, submitted by the sponsor on June 20, 2008 and further revised by the review division on September 3, 2008.

3 DISCUSSION

The purpose of Medication Guides is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor, follows the approved Ambien MG, and has a Flesch Kincaid Grade level of 8.2 and a Flesch Reading Ease score of 58.6%. The sponsor's proposed PIFU has a Flesch Kincaid Grade level of 7.8 and a Flesch Reading Ease Score of 58.6%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised PIFU has a Flesch Kincaid grade level of 5.9 and a Flesch Reading Ease score of 74.8%.

In our review of the MG, we have:

- ensured that the proposed ZolpiMist MG is consistent with the currently approved Ambien MG, with the exception of minor product specific differences.
- simplified wording and clarified concepts where possible,
- made the MG and PIFU consistent with the PI,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.

- ensured that the MG and PIFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG and PIFU. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG and PIFU.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The submitted ZolpiMist MG is consistent with the approved Ambien MG unless otherwise indicated here and in the MG.
2. The RD should clarify whether the product will be called ZolpiMist (zolpidem tartrate) Oral Spray _____ This is unclear from looking at the top of the PI. b(4)
3. The MG for ZolpiMist is a class MG; however, Ambien has a real risk of hypersensitivity; whereas the risk is thought to be theoretical with ZolpiMist. If risk of hypersensitivity is theoretical with ZolpiMist, under PLR labeling format, hypersensitivity should not be listed as a contraindication to use. In that case, the section "Who should not take ZolpiMist?" should be deleted from the Medication Guide. The language in the MG must be consistent with the language in the PI. DRISK notes that this may present issues with the other approved sedative-hypnotics with the insomnia indication, in the class, as well as the 505 (b) (2) products that will be reviewed in the near future.
4. Under the most common side effects, the paragraph "After you stop taking a sleep medicine..." does not mention fatigue. Fatigue is listed in the Ambien label, as well as in the ZolpiMist label, but is missing from both MGs. We have added it here as "tiredness." Ironically, trouble sleeping is listed above; however, insomnia is not listed in the PI in section 9.3 with the list of withdrawal symptoms for both Ambien and ZolpiMist. We recommend that the RD look at this section for Ambien and the other sedative-hypnotics with the insomnia indication that have the class MG, and correct it as needed.
5. ZolpiMist is a (C-IV) controlled substance that is provided in a metered-dose bottle and does not have a child-resistant container closure. The sponsor should provide instruction for safe disposal of ZolpiMist bottles that are empty or no longer needed. Sponsor is going to child resistant
6. In The Ambien PI, Section 17 Patient Counseling Information includes a subsection 17.3 Administration Instructions, which includes information for healthcare providers to counsel patients about administration of the product. This

is followed by subsection 17.4 Medication Guide. The Medication Guide is appropriately referenced at the top of section 17.

In the proposed ZolpiMist PI, section 17 Patient Counseling Information includes a subsection 17.3 Administration Instructions, that also includes information for healthcare providers to counsel patients about administration of the product. However, detailed Patient Instructions for Use are included here. This is followed by section 17.4 Medication Guide.

We recommend moving the Patient Instructions for Use from subsection 17.3 to the end of section 17.4, as an addendum to the MG. Subsection 17.4 should be called FDA-Approved Patient Labeling (Medication Guide). FDA-Approved Patient Labeling should also be referenced as section 17.4 in the PI Table of Contents.

7. In the PIFU:

- The sponsor should add a labeled figure showing the parts of the spray device. All figures should be labeled and referenced in the text.
- We have revised the priming instructions to be more patient-friendly.
- The sponsor should clarify if instructions are needed to clean and maintain ZolpiMist. If so, add to the PI and PIFU. The sponsor should also address in the PI and PIFU what patients should do if ZolpiMist does not work correctly (malfunctions). The sponsor might refer to the Patient Instructions for Use for some of the approved nasal sprays for possible examples.
- We added the statement: See Medication Guide section "How should I store ZolpiMist?" for instructions about how to store ZolpiMist.

- 8. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208. In particular, the carton and container labels must comply with 21 CFR208.24 (a) (2) (d). We are not able to locate submission of revised labels in the EDR.**

Please let us know if you have any questions.

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Sharon Mills
9/10/2008 09:22:07 AM
DRUG SAFETY OFFICE REVIEWER

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