



**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 5, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products, HFD-120

Through: Kellie Taylor, Pharm.D., MPH, Team Leader
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Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis, HFD-420

From: Tara Turner, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis, HFD-420

Subject: Proposed Child-Resistant Packaging Review

Drug Name(s): ZolpiMist (Zolpidem Tartrate) Oral Spray
5 mg (100 microliters) per spray

Application Type/Number: NDA # 22-196

Applicant: NovaDel Pharma, Inc.

OSE RCM #: 2008-1503

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EXECUTIVE SUMMARY

Our assessment of the proposed child-resistant container (CRC) packaging identified several areas of vulnerability that could lead to medication error. We found that the proposed CRC packaging impedes the visibility of the immediate container label, the instructions for cap removal are difficult to read, and the patient instructions for use do not include directions for removal and replacement of the CRC cap. Additionally, the inclusion of the clear plastic cap, which covers the spray nozzle, provides the opportunity for patients to neglect to use the child-resistant container closure. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

We request that the applicant submit revised labels, labeling, and packaging for our review prior to marketing.

Additionally, we note that the proprietary name, ZolpiMist, should be re-reviewed 90 days prior to approval. It is our understanding that an action may occur in late December. Given the recency of OSE review # 2007-2495, which was signed on August 31, 2008, we recommend those conclusions regarding the acceptability of the name ZolpiMist be considered final. However, if action does not occur by January 1, 2009, please resubmit the name for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products (HFD-120) to evaluate the ZolpiMist proposed child-resistant container closure for the potential to contribute to medication errors.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) completed a proprietary name, label, and labeling review for ZolpiMist (OSE RCM #2007-2495) on August 31, 2008 in which we identified a concern regarding the potential for accidental exposure due to lack of a child-resistant container closure. As discussed in that review, we informally contacted the Consumer Product Safety Commission (CPSC) and learned that, according to 16 CFR 1700.14(a)(4) and 1700.14(a)(10), this product will require a child resistant container closure because it is both a prescription drug for oral administration and a controlled drug for oral administration. During a teleconference with the applicant, held on August 6, 2008, we were informed that they had consulted directly with the CPSC regarding this issue. Subsequently, the applicant submitted a description and technical drawings of the proposed child resistant packaging for ZolpiMist, as well as a working sample

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1.3 PRODUCT INFORMATION

ZolpiMist (zolpidem tartrate) Oral Spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The product is designed to be sprayed directly into the mouth over the tongue. Each metered actuation delivers 5 mg of zolpidem in 100 microliters. The recommended dose for adults is 10 mg (2 sprays) immediately before bedtime. The product is available in a amber glass bottle with a metered-dose pump assembly and clear over cap. Each bottle contains 8.2 g of product formulation. There are 60 metered actuations per bottle after 5 initial priming actuations. However, the total number of available doses is dependent on the number of actuations per

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dose (1 or 2 actuations) and the frequency of priming. The applicant proposes that ZolpiMist be classified as Schedule IV consistent with all currently approved zolpidem drug products and the related class of benzodiazepine drug products.

ZolpiMist is a 505(b)(2) application. The reference listed drug is Ambien (zolpidem tartrate) tablets (NDA 19-908), which was approved on December 16, 1992. Ambien is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The usual recommended dose is 10 mg once daily immediately before bedtime. The product is available as 5 mg and 10 mg tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PACKAGING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because medication error prevention staff analyze reported misuse of drugs, we staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

We reviewed two amendments which were submitted by the applicant as follows:

- Amendment SN 0010 – submitted August 15, 2008 – The applicant committed to develop child-resistant packaging for ZolpiMist prior to commercial marketing.
- Amendment SN 0016 – submitted September 12, 2008 – The applicant provided a description and technical drawings of the proposed child-resistant container closure (see Appendices A, B, C, and D for technical drawings).

We also reviewed a working sample of the proposed child-resistant container closure, which was submitted by the applicant on September 17, 2008 (see Appendix E for photograph).

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

3.1 PACKAGING DESCRIPTION

The proposed child-resistant packaging for ZolpiMist is a polypropylene, two-part packaging system consisting of a base and a cap. The base is designed to hold the primary container (pump and bottle containing the formulation) in a manner that prevents manual disassembly, effectively making the base part of the primary packaging configuration. The cap is designed to be child-resistant. This is accomplished by a three-step process for removal of the cap (see Appendix C).

The child resistant feature of the proposed packaging does not come in contact with the product formulation or functional aspects of the pump and, therefore, will have no impact on product stability or pump performance.

3.2 PACKAGING RISK ASSESSMENT

Review of the proposed child-resistant packaging identified several areas of vulnerability that could lead to medication error, specifically with respect to proper identification of the product, instructions for use, and child-resistant storage.

Immediate Container

The label on the original immediate container will not be visible once it is packaged in the proposed child-resistant configuration.

The opening instructions located on top of the child-resistant cap, as well as the arrows on the sides, are debossed in the same color as the cap (i.e. blue).

The proposed child-resistant configuration includes the original clear plastic cap which covers the spray nozzle, in addition to the child-resistant cap.

Patient Instructions for Use

The current patient instructions for use do not include the steps for removing and replacing the proposed child-resistant cap, nor do they include information regarding the importance of storing the product with the child-resistant cap attached.

The current patient instructions for use do not include diagrams of the proposed child-resistant packaging.

4 DISCUSSION

In our assessment we found that the proposed child-resistant container closure impedes the visibility of the immediate container label. In our review of the technical drawings of the child-resistant packaging there is no indication of where the container label will be displayed. However, we note that on the working sample that was submitted, the container label is appropriately displayed around the outside of the package base, so that even if the child-resistant cap is removed, the product remains properly labeled to promote safe use. If the label does in fact appear on the outside of the CRC packaging, then this is acceptable.

We also note that the instructions for cap removal, which are located on top of the child-resistant cap, as well as the arrows on the sides, are debossed in the same color as the cap (i.e. blue). This presentation does not provide optimal contrast, which makes the information difficult to identify and read.

The current patient instructions for use do not include instructions for removal and replacement of the child-resistant cap, nor do they include diagrams of the child-resistant packaging configuration. It is important that the product labeling reflect the final approved packaging configuration to avoid confusion

and to aid patients in using the product. Similarly, the patient instructions for use should highlight the importance of storing the product with the cap attached to the base in order to maintain the child-resistant mechanism.

Finally, the working sample contains the clear plastic cap from the original container which covers the spray nozzle opening. We are concerned that if the clear cap remains with the child-resistant packaging, patients may assume that they can simply cover the product with this cap to achieve child-resistance rather than store it with the child-resistant cap attached. We contacted the chemistry reviewers via e-mail dated September 17, 2008 to find out if removing the clear plastic cap would impact the stability of the product formulation. They responded that this is a possibility and that they do not have any data about product stability without the clear cap.

5 CONCLUSIONS

The Packaging Risk Assessment findings indicate that information presented on the child resistant packaging and in the insert labeling and patient instructions for use is vulnerable to confusion that could lead to medication errors with ZolpiMist. Additionally, the inclusion of the clear plastic cap, which covers the spray nozzle, provides the opportunity for patients to neglect to use the child-resistant container closure.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the proposed child-resistant packaging, the Division of Medication Error Prevention and Analysis has identified areas of needed improvement. We have provided specific recommendations in Section 6.2. We request this information be forwarded to the applicant.

In order to ensure safe use of this product, it is important for the labels and labeling to accurately reflect the final packaging configuration. However, the applicant's proposal to submit this information as a CBE-0 post-approval may not afford the Agency an opportunity to review the revised container label, insert labeling and patient instructions for use to ensure they are not vulnerable to confusion leading to medication errors. Therefore, we request that the applicant submit revised labels, labeling, and packaging for our review prior to marketing.

Additionally, we note that the proprietary name, ZolpiMist should be re-reviewed 90 days prior to approval. It is our understanding that an action may occur in late December. Given the recency of OSE review # 2007-2495, which was signed on August 31, 2008, we recommend those conclusions regarding the acceptability of the name ZolpiMist be considered final. However, if action does not occur by January 1, 2009, please resubmit the name for evaluation.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

6.2 COMMENTS TO THE APPLICANT

A. Immediate Container

Position the container label on the outside of the product base, as presented on the working sample, to ensure that the product information remains visible, allowing the product to be properly identified at all times.

B. Child Resistant Container Cap

1. For the opening instructions located on top of the child-resistant cap and the arrows located on the sides, revise the color of the debossed lettering to black or some other color that provides greater contrast and improved readability.
2. Since it is our understanding that the stability of the product has not been studied without the clear plastic cap, indicate, via debossed lettering, that the clear plastic cap is not child-resistant. As currently designed with this plastic cap, the product can be stored without the use of the CRC closure. Placing the statement on the cap will help to decrease the risk of omitting the child-resistant cap when the product is stored.

C. Insert Labeling and Patient Instructions for Use

1. Incorporate the instructions for cap removal and replacement into the current patient instructions for use. Modify the product diagrams to be consistent with the proposed packaging.
2. In both the insert labeling and the patient instructions for use, highlight the importance of storing the product with the child-resistant closure cap attached to the base in order to maintain the child-resistant mechanism. The professional and patient labeling should also note that the clear immediate container cap is not child-resistant.

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Draft Labeling (b5)

Deliberative Process (b5)

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Tara Turner
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**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEETING DATE: September 17, 2008

MEETING PURPOSE: Telecon Meeting to Provide Notification of 3-month Extension of PDUFA Action Date for Zolpimist NDA 22-196

APPLICATION: Zolpimist Oral Spray NDA 22-196

SPONSOR: NovaDel Pharma Inc.

INDICATION: Short-term treatment of insomnia characterized by difficulties with sleep initiation

MEETING CHAIRS: Russell Katz, FDA: _____

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MEETING RECORDER: _____, Cathy Michaloski PM
DNP

PARTICIPANTS:

FDA Attendees (Division of Neurology Drug Products):

Russell Katz, M.D., Director
Devanand Jilapalli, M.D., Medical Team Leader
Cathleen Michaloski MPH, Regulatory Project Manager

Sponsor Attendees:

NovaDel Pharma Inc.
David Bergstrom, Ph.D., Chief Operating Officer and Sr. Vice President
Enrique Dilone, Ph.D., Executive Director, Quality and Analytics
NovaDel Pharma Inc. Advisor

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The teleconference was convened to provide notification to NovaDel that the FDA review of Zolpimist NDA 022196 is almost completed, but that the Division was recently made aware that a clinical study site inspection (on pivotal BE studies & _____) was conducted and a Form FDA-483 was issued which, according to the inspector, raised potentially significant questions on the way the studies were conducted and around the reliability of the data. The _____ response, which

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was submitted to the FDA District Office in Atlanta, is currently under discussion by the Division in collaboration with the FDA inspection team and more time is needed for completion of the review.

The Zolpimist NDA PDUFA Date was Sunday, September 21, 2008, (effectively, Friday, September 19, 2008) but the _____ response and the issues raised are considered by the Agency to be substantive documents that need to be reviewed before the Agency can take action on the NDA. Therefore, the Zolpimist NDA PDUFA review clock will be extended to give both the Division and the inspection team a chance to fully review the issues and response.

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_____ asked what the next steps were and if FDA needed anything further from NovaDel at this point. Dr. Katz replied that the FDA review of the rest of the Zolpimist NDA is complete and the labeling review is in final stages. The Division will continue to negotiate labeling with NovaDel in the near future.

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Once that is done, and issues on the FDA Form 483 are resolved, FDA would likely act on the application prior to the 3 month PDUFA extension date (Dec 21, 2008).

Summary by sponsor and Division PM.

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