

The sponsor as represented by Dr. Uma Arumugam, warranted that the search and results are accurate. Below is a summary of the search results upon examination:

- Among the 145 articles, only 27 articles were considered relevant to zolpidem PK, efficacy, and safety and were reviewed based on 9 areas, most of which were the search terms. The sponsor concludes, "No new relevant publications were identified as a result of this expanded keyword search, with the exception of one case study involving drug interactions (Kito, 2006)." –(See the case below.)
- The Kito article reveals a possible fluvoxamine-zolpidem interaction in an 82 year-old woman who was on 150mg/day of fluvoxamine and 10mg of zolpidem. Her visual hallucination and amnesia disappeared after zolpidem was discontinued. According to the report, the patient's comprehensive blood tests, EEG, and MRI of the brain all showed normal results– It's a possible case though this senior patient was given a higher dose, 10mg instead of 5mg, and there is no information on if her symptoms persisted while she was given a more appropriate lower dose.
- One case report presents the QT-prolongation and torsades de pointes reported in a 67 year-old woman who has history of congestive heart failure and prosthetic mitral valve while on zolpidem 10mg and other cardiovascular medications such as captopril, furosemide, warfarin, and amiodarone. The QTc interval was back to initial value once zolpidem discontinued. – It is a possible case but the patient's medical history is certainly a confounding factor as it could be unstable at times. Further cases/data are needed should addition to the labeling be considered.
- An article reported three cases with compulsive behavior, such as compulsive cleaning or eating after taking the medication. –These patients also had amnesia the next morning. Thus, they seem to be part of the amnesic complex behaviors already described in the labeling, though may seem more of compulsive pattern.
- The author of the above article also raises the issue of adverse reaction rate occurring more common in females, which echoed with a commentary article from Poland regarding gender influences on adverse reaction rates with zolpidem. –More definitive study maybe needed to consider if it should be reflected in the labeling.
- Comparing the AE listing of Ambien labeling, the sponsor found no other unreported AE otherwise.
- No literature reports regarding fatalities, overdose, suicidal ideation or behavior.

9.2 Labeling Recommendations

The sponsor submitted draft labeling essentially based on that of zolpidem tartrate. I agree with Maternal Health Team's suggestions on the Labeling. I also agree most of the items pointed out by the SEALD team including changing adverse experiences and adverse events unanimously to "adverse reactions." I will not repeat these suggestions here but would like to point out a few additional changes:

9.2.1 Section of HIGHLIGHTS

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9.2.2 Section of FULL PRESCRIPTION INFORMATION

1) In the subsection 3 DOSAGE FORMS and STRENGTHS, I suggest adding "artificial cherry flavored" in front of the word "solution" so that people can be aware of the flavor of the mist that most supposed to taste upon getting the spray.

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9.3 Advisory Committee Meeting

Not planned.

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Maternal Health Team Review

Date: August 21, 2008 **Date Consulted:** July 31, 2008

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Through: Karen Feibus, MD
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Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Drug Oncology Products (DDOP)

Drug: ZolpiMist (zolpidem tartrate) Oral Spray; NDA 22-196

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of ZolpiMist labeling.

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of labeling.

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INTRODUCTION

On November 20, 2007, NovaDel Pharma, Inc. submitted a new 505(b)(2) application for ZolpiMist (zolpidem tartrate) Oral Spray (NDA 22-196). The sponsors proposed indication for ZolpiMist is for the short-term treatment of insomnia characterized by difficulties with sleep initiation. On July 31, 2008, the Safety Endpoints and Labeling Development (SEALD) Team requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of ZolpiMist labeling. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of ZolpiMist labeling.

BACKGROUND

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of ZolpiMist labeling.

SUBMITTED MATERIAL

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

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RECOMMENDATIONS

Provided below are MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

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 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for ZolpiMist is provided on pages 3-4 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A – Track Changes Version of Labeling

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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