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*APPLICATION NUMBER:*

**22-196**

# SUMMARY REVIEW

**MEMORANDUM**

DATE: December 15, 2008

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-196

SUBJECT: Action Memo for NDA 22-196, for the use of Zolpimist (zolpidem tartrate) metered oral spray

NDA 22-196, for the use of Zolpimist (zolpidem tartrate) metered oral spray, for the treatment of insomnia, was submitted by NovaDel Pharma, Inc., on 11/20/07. This is a 505(b)(2) application, with Ambien as the reference listed drug. The application contains the results of several pharmacokinetic studies designed to demonstrate bioequivalence between Zolpimist oral spray and Ambien, as well as assessments of several pharmacodynamic effects. Each metered spray dispenses 5 mg of zolpidem tartrate.

The application has been reviewed by Dr. June Cai, medical officer, Dr. Jagan Parepelly, Office of Clinical Pharmacology, Dr. Shastri Bhamidipati, chemist, Dr. Melissa Banks, pharmacologist, Dr. Sriram Subramaniam, Division of Scientific Investigations, Dr. Richardae Araojo, Pediatric and Maternal Health Staff, Dr. Tara Turner, Division of Medication Error Prevention and Analysis, Sharon Mills, Division of Risk Management, Dr. Silvia Calderon, Controlled Substances Staff, and Dr. Devanand Jillapalli, Neurology Team Leader. Dr. Jillapalli and the clinical team recommend that the application be approved, although staff of the Division of Scientific Investigations recommends that the application not be approved at this time. I will briefly review the relevant issues and offer the rationale for the division's action.

The sponsor has conducted two definitive bioequivalence studies, one each in healthy young adults and elderly adults. Both studies document the bioequivalence of Zolpimist and Ambien, 5 mg and 10 mg (the dose in the elderly is 5 mg; the dose in younger adults is 10 mg). Although subjects receiving Zolpimist perform more poorly on the DSST 13 minutes after dosing than subjects receiving Ambien, at 23 minutes after dosing, the responses are similar with both treatments at 23 minutes (the Tmax of Zolpimist is slightly shorter than with Ambien). The differences seen at 13 minutes are clinically of no import, because the drug is taken just before bed, and is designed to induce sleep.

There are no significant differences in the safety profiles of Zolpimist and Ambien.

There are no outstanding chemistry issues. Although the file contains discussions related to the sponsor's ***intention*** to produce child-resistant packaging, they have already done so to our satisfaction. b(4)

This is acceptable, and will not preclude approval at this time.

As noted by Dr. Jillapalli, the major issue in this application is the finding by DSI investigators of several significant deficiencies. Specifically, DSI found numerous irregularities related to documentation of study conduct. For example, they documented instances of drug administration that were retrospectively changed. Other findings included discrepancies between the times of plasma sampling and assays run on those samples, or storage times (for example, in some cases, storage times were earlier than sampling times). Other problems were also noted (see, for example, Dr. Jillapalli's listings, pages 11 and 12, and the DSI review). The sponsor responded to these concerns, but DSI staff found the sponsor's responses inadequate.

However, as Dr. Jillapalli has noted, DSI performed a 100% audit of the study, and identified all significant deficiencies. As a result, data from those patients with discrepancies in their records were removed, and the bioequivalence studies (primarily the study in healthy younger adults; there were very few problematic findings in the study of healthy elderly subjects) were re-analyzed. When Dr. Parepally excluded the data from these subjects, Zolpimist was still seen to be bioequivalent to Ambien.

Staff of DMEPA have found the proposed tradename to be acceptable.

Because Zolpimist is a hypnotic drug, it will be required to adopt class language pertaining to the risk of complex behaviors during sleep and allergic reactions to be included in a Medication Guide. In addition, the Medication Guide will contain sections that will describe in detail how the product is to be used by patients. Because there is a Medication Guide, the sponsor has been asked to submit a Risk Evaluation and Mitigation Strategy (REMS). They have done so, and it is acceptable.

Finally, Dr. Calderon of CSS has expressed concerns related to the potential of Zolpimist to result in an increase in abuse compared to Ambien, because it is a concentrated oral formulation (50 mg/mL), it is sweet and flavored, and, given that it is a multi-dose spray (can deliver up to 60 sprays), multiple doses can be easily administered. In response to these concerns, the sponsor has proposed an intensified post-marketing monitoring plan, the specifics of which are described by Dr. Calderon (page 2 of her 11/25/08 review), and which she finds acceptable.

**Comments**

**Zolpimist is bioequivalent to Ambien. There are no safety issues that would preclude its approval. Although DSI has found numerous and significant deficiencies in their inspection of a pivotal bioequivalence study, I agree with Dr. Jillapalli that the study is still acceptable, given that all deficiencies were identified, and exclusion of the questionable data still reveals the products to be bioequivalent. This disagreement has been discussed with DSI staff, who accepts our decision to approve this application.**

**For these reasons, then, I will issue the attached Approval letter.**

**Russell Katz, M.D.**

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/s/
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Russell Katz
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