

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review Memo

Date	12/7/08
From	Devanand Jillapalli, MD
Subject	Team Leader Review Memo
NDA/BLA #	N 22196
Applicant	NovaDel Pharma Inc
Date of Submission	11/20/07
PDUFA Goal Date	12/21/08
Proprietary Name / Established (USAN) names	Zolpimist / Zolpidem tartrate oral spray
Dosage forms / Strength	Metered dose oral spray (5 mg per 100 µL spray)
Proposed Indication(s)	Short-term treatment of insomnia characterized by difficulties with sleep initiation
Recommended:	Approval

1. Introduction

On 11/20/07, NovaDel Pharma Inc. submitted a 505(b)2 NDA application (#022196) for Zolpimist Oral Spray containing the active ingredient zolpidem tartrate indicated for the short term treatment of insomnia characterized by difficulties with sleep initiation. Zolpimist is a metered dose oral spray (new dosage form and new route of administration) with each actuation delivering 5 mg of zolpidem tartrate in 100 µL. Thus, one spray delivers 5 mg and two sprays 10 mg of zolpidem tartrate, and is designed to be bioequivalent to the 5 mg and 10 mg tablets of the reference listed drug, Ambien (zolpidem tartrate). In addition to the four pharmacokinetics studies, NDA 022196 is supported by reference to the approved Ambien NDA 019908 and published literature. The proposed label is identical to the approved reference listed drug (Ambien) label with the following exceptions: description of the PK results of the bioequivalence studies, formulation, drug administration (including instruction to the patient), manufacturing and packaging. The sponsor is not seeking any new efficacy claims.

2. Background

Ambien (zolpidem tartrate) was approved on 12/16/92 for the short-term treatment of insomnia characterized by difficulties with sleep initiation under NDA 019908. The sponsor's clinical rationale for developing Zolpimist is:

- Effective alternative for patients who experience difficulty in swallowing oral tablets, or who are restricted from taking anything by mouth, or those who suffer from gastric stasis.

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- As an option in the general population because of the convenience and ease of use (no need for administration with water).

A pre-IND meeting on was held 8/31/05, which is referred to in relevant sections of this review. There was no pre-NDA meeting.

The original PDUFA due date was 9/21/08. However, on 9/12/08, the Division of Neurology Products (DNP) received from DSI an evaluation of Form 483 items. The DSI report concluded that multiple issues concerning incomplete or contradictory documentation with respect to dosing, PK sample handling and drug accountability, fail to assure the reliability of source data generated in the pivotal bioequivalence studies (Studies 003 and 004). Further, DSI was currently evaluating _____, response to Form 483. After completing this review, DSI was expected to forward a summary of evaluation to DNP. Please see section 11 of this review memo for further details and discussion. Therefore, on 9/21/08, DNP communicated to the sponsor that additional time was necessary for a substantive review of the issues raised by DSI inspection, and therefore, the NDA PDUFA review clock was extended by 3 months to 12/21/08.

b(4)

3. CMC/Device

Dr. Shastri Bhamidipati was the CMC reviewer. In his memo dated 9/16/08, Dr. Ramesh Sood (Branch Chief, ONDQA) writes that all CMC related issues had been resolved for this application, and that this application is recommended for Approval from CMC perspective. There are no major issues that would preclude the approvability of the product. There are no phase IV requirements or commitments for CMC.

Child-resistant packaging: During internal discussions, there were concerns regarding the lack of child-resistant packaging. Although, the enforcement of the applicable statutes regarding child-resistant packaging resides with the Consumer Product Safety Commission (CPSC), the Division discussed this issue with the sponsor on 8/6/08 (Telecon). During this Telecon, the sponsor confirmed that there will be child-resistant packaging in compliance with CPSC requirements. Via email on 9/9/08, Ms. Donna Katz from the Agency's Office of the Chief Counsel stated that _____

b(5)

_____ On 9/12/08, the sponsor sent information to the NDA on the prototype of the proposed child-resistant packaging including the results of preliminary testing of this prototype in children _____

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_____ The regulatory oversight of the technical aspect of child-resistant packaging will be deferred to CPSC. However, Dr. Bhamidipati, in his review of 9/16/08, concludes that the CR packaging is completely external

to primary packaging and thus there is no impact on product quality attributes and pump performance from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

Dr. Melissa Banks was the pharmacology/toxicology reviewer. Dr. Bank's final review is pending.

In response to the Division's request at the pre-IND meeting on 8/31/05, the sponsor conducted a repeat-dose, oral irritation study in rats using Zolpimist (doses up to 20 mg) for 1 month.

5. Clinical Pharmacology/Biopharmaceutics

Dr. J. M. Parepally was the clinical pharmacology reviewer.

A total of 4 PK studies were conducted in healthy volunteers. Of these, two were pilot PK studies (Study 001 and Study 002), and two were definitive bioequivalence PK clinical studies (one in healthy non-elderly adults – Study 003; and the other in healthy elderly subjects – Study 004).

- Study 001 was a single-center, active-controlled (Ambien), open-label, dose-ranging PK crossover study in 10 healthy male (18-40 years) volunteers. Subjects received a single dose of each of the four treatments (Ambien 10 mg; Zolpimist 2.5 mg; Zolpimist 5 mg; Zolpimist 10 mg) following an overnight fast in a predetermined sequence with a washout period of 7 ± 3 days. Blood samples were collected at multiple time points.
- Study 002 was a single-center, 5-way crossover, open-label, dose-ranging, multiple-treatment PK crossover study in 14 healthy male (18-45 years) volunteers. Subjects received a single dose of each of the five treatments [Ambien 10 mg (fasting); Zolpimist 10 mg (fasting); Zolpimist 5 mg (fasting); Ambien 5 mg (fasting); Zolpimist 10 mg (fed)] in a predetermined sequence with a washout period of 7 ± 3 days. Subjects were instructed not to swallow for a period of 30 seconds and to avoid intentional swallowing for up to 5 minutes following dosing, if possible. Blood samples were collected at multiple time points.
- Study 003 was a single-center, 4-way crossover, open-label, dose-ranging, multiple-treatment PK crossover study in healthy male ($n=20$) and female ($n=23$) volunteers, aged 18-45 years. The four treatments were: Zolpimist 5 mg; Ambien 5 mg; Zolpimist 10 mg; and Ambien 10 mg. Subjects were randomly assigned to receive each of the four treatments in 1 of 4 unique treatment sequences, each treatment separated by a washout period of 7 ± 3 days. Subjects were instructed not to swallow for a period of 30 seconds and to avoid intentional swallowing for up to 5 minutes following dosing, if possible. Blood samples were collected at multiple time points.

- Study 004 was a single-center, 2-way crossover, open-label, multiple-treatment PK crossover study in healthy elderly male (n=6) and female (n=18) volunteers, aged ≥ 65 years. The two treatments were: Zolpimist 5 mg; and Ambien 5 mg. Subjects were randomly assigned to receive each of the four treatments in 1 of 2 unique treatment sequences, each treatment separated by a washout period of 7 ± 3 days. Subjects were instructed not to swallow for a period of 30 seconds and to avoid intentional swallowing for up to 5 minutes following dosing, if possible. Blood samples were collected at multiple time points

Dr. Parepally's review finds that based on the two definitive bioequivalence studies (Study 003 and Study 004) Zolpimist 5 mg and 10 mg lingual spray were bioequivalent to the reference Ambien tablets. The 90% confidence interval of the geometric mean ratios for the primary PK parameters (C_{max} and AUC) were contained within the pre-specified intervals of 80-125%. Specifically, Study 003 conducted in healthy *non-elderly* adults comparing Zolpimist 5 and 10 mg spray, and Ambien 5 and 10 mg tablets, demonstrated that all Zolpimist treatments were bioequivalent to Ambien 10 mg tablet. Study 004 conducted in healthy *elderly* adults demonstrated that Zolpimist 5 spray was bioequivalent to the Ambien 5 mg tablet.

Study 001 demonstrated that when normalized for dose, Zolpimist demonstrated a linear relationship to dose for mean C_{max} and $AUC_{0-\infty}$ for 2.5, 5 and 10 mg doses. Study 002 evaluated Ambien 10 mg (fasting), Zolpimist 10 mg (fasting), Zolpimist 5 mg (fasting), Ambien 5 mg (fasting) and Zolpimist 10 mg (fed). However, the study failed to demonstrate bioequivalence for all Zolpimist treatments compared to the Ambien 10 mg; the sponsor attributes this result to the small sample size. Further, Study 002 showed that Zolpimist when given with food significantly decreased C_{max} and AUC by approximately 50% when compared to the fasted state, and prolonged T_{max} to 3 hours from 30-37.5 minutes.

New metabolites: During the pre-IND meeting on 8/31/05, the Division told the sponsor that it expects an analysis of blood samples from PK study subjects to demonstrate that oral mucosal absorption does not lead to the formation of new metabolites which are not encountered via the GI (tablet) route. Dr. Parepally's review concludes that no new metabolites were encountered when zolpidem was absorbed via oral mucosa.

Time to first detectable concentration and ≥ 20 ng/mL: Zolpimist In Study 003 and Study 004, the results for the time to the first detectable concentration and ≥ 20 ng/mL was significantly shorter for Zolpimist as compared to Ambien, as can be seen in the following tables.

Time to (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg	Zolpidem LS 5 mg	Ambien Tablet 10 mg	Zolpidem LS 10 mg	Ambien Tablet 10 mg
First Detectable Concentration	7.0	17.4	7.0	15.3	6.5	15.3
	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
≥ 20 ng/mL Concentration	22.7	27.2	22.7	23.3	17.0	23.3
	$p < 0.0001$		$p = 0.0015$		$p < 0.0001$	
Data represent the means of the time to first detectable concentration and time to a concentration ≥ 20 ng/mL. Cross-reference: Table 14.2.5; Appendix 16.1.9.2.1.11						

Source: NDA Submission, Study 003 report, Table 11.10, p 56

Table 11.10 Analysis of Time to Detectable and ≥ 20 ng/mL Concentrations		
Time to (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg
First Detectable Concentration	5.8	14.6
	$p < 0.0001$	
≥ 20 ng/mL Concentration	13.1	24.0
	$p < 0.0001$	
Data represent the means of the time to first detectable concentration and time to ≥ 20 ng/mL concentration. p -Values are from ANOVA. Cross-reference: Table 14.2.5; Appendix 16.1.9.2.1.11		

Source: NDA Submission, Study 004 report, Table 11.10, p 47

Pharmacodynamics: In Study 001 and Study 002, PD effects of drowsiness/alertness were self-assessed using a scale of 1-5 (5 is much more alert) in Study 001, and Stanford Sleepiness Scale (SSS; scale of 1 to 7, where 1 is wide awake, 7 is no longer fighting sleep) and Digit Symbol Substitution Test (DSST; scored 0-90, with lower scores representing worse performance indicative of less attention) in Study 002, before dosing and at various time points after dosing. In Study 001, there was significantly greater degree of drowsiness with Zolpimist 10 mg than Ambien 10 mg at 15 minutes postdosing (mean score 1.9 versus 2.8; $p = 0.023$), but not at other post dosing time points (30 and 60 minutes). In Study 002, the results show that with the exception of the fed state, no significant differences were noted for SSS scores between any treatment comparisons at any time point. The DSST scores for zolpidem LS 10 mg (fasted) were significantly lower (less attentive) than those for zolpidem LS 10 mg (fed) and Ambien 10 mg (fasted) at 28 minutes after dosing.

In Study 003 and Study 004, subjects performed the DSST within 15 minutes prior to dosing and at 13 and 23 minutes after dosing. DSST results based on inclusion of data from all the treatment periods show that at 13 minutes post dosing both the Zolpimist 5 mg and 10 mg doses produced significantly greater decreases (less attentive) in DSST scores compared to Ambien ($p = 0.005$ and < 0.001 , respectively) but not at 23 minutes post dosing (p -values, 0.680 and 0.081, respectively). Similar results were seen in Study 004: at 13 minutes post dosing Zolpimist 5 mg produced significantly greater decreases in DSST scores compared to Ambien ($p = 0.033$) but not at 23 minutes post dosing ($p = 0.270$).

The above PD results are discussed further under safety section 8 of this review.

Re-analysis following DSI inspection report: DSI found specific instances of documentation discrepancies with regard to dosing and PK sample handling in their 100% clinical audit that question the data generated at these specific time points. Dr. Parepally, in his Addendum to Clinical Pharmacology and Biopharmaceutics Review, re-analyzed Study 003 for

bioequivalence after excluding the data from the following subjects at specific time points obtained from Form 483 (issued on 8/7/08) and DSI report:

Study NVD-ZOLP-PH- 003			
Clinical Issues			
Subject #	Period	Problems	Reviewer Comments
1	4	Switched information(example A10 to Z 10) 24 days later	Excluded from analysis
2	4	Switched information 24 days later	Excluded from analysis
4	4	Switched information 24 days later	Excluded from analysis
12	4	Switched information(A10 to Z 10) 24 days later. Vomited 45 min post dose.	Cannot be verified, Excluded
13	4	Switched information(A10 to Z 10) 24 days later	Cannot be verified, Excluded
28		Dates in CRF does not match with dosing records	Excluded from analysis
22 through 25	2	PK sampling discrepancy in records (Recorded as processing sample before actual sampling)	Excluded from analysis
Analytical Issues			
Study NVD-ZOLP-PH- 003			
1 through 8	4	QCs failure in runs	Excluded from analysis
9	4	Sample switching between aliquot A and B (11 Samples)	Excluded from analysis
23	3	Sample switching between aliquot A and B (11 samples)	Excluded from analysis
40	3	30 min sample, Sample switching between aliquot A and B	Excluded from analysis
41	3	30 min sample, Sample switching between aliquot A and B	Excluded from analysis
44	2	Sample switching between aliquot A and B (11 Samples)	Excluded from analysis
26		90 min sample processing record discrepancy	Excluded from analysis

The original analysis of Study 003 included 43 subjects. Re-analysis following DSI report included 37 subjects of which 22 subjects had data for all the periods of the study. In this re-analysis, Dr. Parepally finds that Zolpimist 5 mg and 10 mg lingual spray were bioequivalent to the reference Ambien tablets. Since only one subject (#24) had had dosing and sample processing records discrepancy, Dr. Parepally did not perform reanalysis of Study 004.

However, Form 483 (issued on 8/7/08) and DSI's final summary evaluation (10/20/08) contained questionable PK data at additional time points for subjects, which were not excluded from Dr. Parepally's re-analysis: Subject 20, 21 and 26 on 1/20/07 (Observation 3), and Subject 12 at period 2 (DSI evaluation 10/20/08). Further, the identity of the six subjects (i.e., 43 minus 37) who were excluded from re-analysis was not clear from Dr. Parepally's re-analysis of Study 003. I discussed these issues with Dr. Parepally on 12/4/08.

Dr. Parepally clarified that the six subjects who were excluded from re-analysis (i.e., all data points) in Study 003 were: # 25, 28, 32, 34, 35 and 47. Dr. Parepally then conducted another analysis after excluding Subject 12 (at both period 2 and 4), and Subjects 20 and 26 (even though only one sample was questionable, since there was no period number mentioned in the 483 observation, these two subjects were not considered at all periods). This additional analysis (see below) shows that Zolpimist 5 mg and 10 mg lingual spray were bioequivalent to the reference Ambien tablets.

Data Re- Analysis - Pivotal BE Study 003 NDA 22196 Zolpimist

C_{max}	%LL	%UL
B vs A	87.559	111.532
C vs A	99.1787	126.208
D vs A	85.2531	108.711

AUC_{0-inf}	%LL	%UL
B vs A	82.6084	105.783
C vs A	92.787	118.696
D vs A	85.3682	109.436

- A Ambien tablet 10 mg (Reference)
- B zolpidem LS 5 mg
- C Ambien tablet 5 mg
- D zolpidem LS 10 mg

Data from Dr. Parepally's email dated 12/4/08

For Study 004, Dr. Parepally states that (email of 12/4/08) even though Subjects 19 through 23 had a protocol deviation of dosing 3 days apart (instead of 7±3 days), it does not have impact on PK since 3 days is good enough for washout (mean half life of zolpidem is 3.1 hrs). I agree with his conclusion. Re-analysis was not conducted since there was only 1 subject (#24) with recording error.

Please see section 11 of this review memo for additional discussion.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

This NDA is based on demonstrating bioequivalence to Ambien, and not on any new efficacy data. The sponsor is not seeking any new efficacy claims.