# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-196**

## MEDICAL REVIEW(S)

# CLINICAL REVIEW[1]

| | |
|---|---|
| Application Type | 505 b (2) NDA |
| Submission Number | 22196 |
| Submission Code | 000 |
| Letter Date | November 20, 2007 |
| Stamp Date | November 20, 2007 |
| PDUFA Goal Date | September 19, 2008 |
| Reviewer Name | June Cai, MD |
| Review Completion Date | August 6, 2008 |
| Established Name | Zolpidem tartrate |
| (Proposed) Trade Name | ZolpiMist™ Lingual Spray |
| Therapeutic Class | Hypnotics |
| Applicant | NovaDel Pharmaceuticals Inc. |
| Priority Designation | S |
| Formulation | Oral Spray |
| Dosing Regimen | 5mg per spray:<br>-Adults: 10mg immediately before bedtime<br>-Elderly: 5mg<br>-With hepatic impairment: 5mg |
| Indication | Short-term treatment of insomnia |
| Intended Population | Adults and elderly |

1 The new full NDA review template is applied to this review as instructed.

## Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT ..... 4

1.1 Recommendation on Regulatory Action ..... 4
1.2 Risk Benefit Assessment ..... 4
1.3 Recommendations for Postmarketing Risk Management Activities ..... 4
1.4 Recommendations for other Post Marketing Study Commitments ..... 4
1.5 Other Phase IV Commitments ..... 4

2 INTRODUCTION AND REGULATORY BACKGROUND ..... 4

2.1 Product Information ..... 4
2.2 Availability of Proposed Active Ingredient in the United States ..... 5
2.3 Currently Available Treatments for Proposed Indication and Important Safety Issues with Consideration 5
2.4 Summary of Presubmission Regulatory Activity Related to Submission ..... 6
2.5 Other Relevant Background Information ..... 6

3 ETHICS AND GOOD CLINICAL PRACTICES ..... 7

3.1 Submission Quality and Integrity ..... 7
3.2 Compliance with Good Clinical Practices ..... 7
3.3 Financial Disclosures ..... 7

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES ..... 7

4.1 Chemistry Manufacturing and Controls ..... 7
4.2 Preclinical Pharmacology/Toxicology ..... 7
4.3 Clinical Pharmacology ..... 7
4.3.1 Pharmacodynamics ..... 8
4.3.2 Pharmacokinetics ..... 8

5 SOURCES OF CLINICAL DATA ..... 9

5.1 Table of Clinical Studies ..... 9
5.2 Review Strategy ..... 9
5.3 Discussion of Individual Studies ..... 10

6 REVIEW OF EFFICACY ..... 11

7 REVIEW OF SAFETY ..... 11

7.1 Methods ..... 11
7.1.1 Clinical Studies Used to Evaluate Safety ..... 11
7.1.2 Adequacy of Data ..... 12
7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence ..... 12
7.2 Adequacy of Safety Assessments ..... 13
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations Explorations for Dose Response ..... 13
7.2.2 Special Animal and/or In Vitro Testing ..... 13
7.2.3 Routine Clinical Testing ..... 13
7.2.4 Metabolic, Clearance, and Interaction Workup ..... 14
7.2.5 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..... 14
7.3 Major Safety Results ..... 14
7.3.1 Deaths ..... 14
7.3.2 Nonfatal Serious Adverse Events ..... 14
7.3.3 Dropouts and/or Discontinuations ..... 14
7.3.4 Other Significant Adverse Events ..... 14

7.3.5 Submission Specific Primary Safety Concerns....14
7.4 Supportive Safety Results....15
7.4.1 Common Adverse Events....15
7.4.2 Special Safety Studies....17
7.4.3 Immunogenicity....17
7.5 Other Safety Explorations....17
7.5.1 Dose Dependency for Adverse Events....17
7.5.2 Time Dependency for Adverse Events....18
7.5.3 Drug-Demographic Interactions....18
7.5.4 Drug-Disease Interactions....18
7.5.5 Drug-Drug Interactions....18
7.6 Additional Safety Explorations....18
7.6.1 Human Carcinogenicity....18
7.6.2 Human Reproduction and Pregnancy Data....18
7.6.3 Pediatrics and Effect on Growth....18
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound....18
7.7 Additional Submissions....19

**8 POSTMARKETING EXPERIENCE....20**

**9 APPENDICES....20**

9.1 Literature Review/References....20
9.2 Labeling Recommendations....21
9.3 Advisory Committee Meeting....22

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

From clinical perspective, I recommend the Division taking an approval action for this NDA supplement if other aspects of data are sufficient, including inspection from the Agency Division of Scientific Inspection.

## 1.2 Risk Benefit Assessment

Despite potential risks, this application appears to demonstrate sufficient benefit outweighing risks if the data quality and reliability are sufficient.

## 1.3 Recommendations for Postmarketing Risk Management Activities

In addition to Medication Guide, periodic postmarketing surveillance for adverse events and abuse potential [redacted] b(4)
(Cross-references: See also subsection 7.6.4 on page 19.)

## 1.4 Recommendations for other Post Marketing Study Commitments

None from clinical point of view.

## 1.5 Other Phase IV Commitments

None from clinical point of view.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

ZolpiMist™ is a new dosage and formulation of zolpidem tartrate (Ambien®) which chemical name is *N,N*,6-trimethyl-2-*p*-tolylimidazo[1,2-*a*] pyridine-3-acetamide L-(+)-tartrate (2:1), a non-benzodiazapine hypnotic of the imidazopyridine class.

It uses a metered dose oral spray delivery system that delivers a 5-mg dose of zolpidem tartrate in a 100uL spray. The sponsor states that one and two of actuations of ZolpiMist™ are intended to correspond with the 5- and 10 mg Ambien tablets. The indication for this product is for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

## 2.2 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is the active ingredient and it is an FDA approved and marketed drug and readily available in the U.S.

## 2.3 Currently Available Treatments for Proposed Indication and Important Safety Issues with Consideration

Below is a list of products that have been approved for this indication since 1970.

**Table 1. FDA Approved Hypnotics (1970-August 5, 2008)**

| Categories | Drug Names | | Significant AEs |
|---|---|---|---|
| Benzodiapapines | Dalmane | flurazepam | Paradoxical effect |
| | Restoril | temazepam | |
| | Doral | quazepam | |
| | Halcion | triazolam | Traveler's amnesia, increased day time anxiety or depression |
| Nonbenzodiazapines | ProSom* | estazolam | Amnesia, sleep driving, bizarre or complex behaviors, esp. when taken with alcohol and or other CNS depressants; Aggression and other disinhibitive behaviors, changes in mood, perceptions, and thought contents; paradoxical effect |
| | Ambien | zolpidem | |
| | Sonata | zaleplon | |
| | Lunesta | eszopiclone | |
| | Ambien CR | zolpidem slow release | |
| | Rozerem | ramelteon | Problems in libido, fertility, and menses or galactorrhea |

*Brand name manufacturing discontinued by the sponsor, Abbott for commercial reasons.

Chloral hydrate (one of the brand names is Noctec) has also been used from very old days for treatment of insomnia as well as sedation. It has been used in both adults and children. Its main issues include cardiac arrhythmias of all forms including prolonged QT, torsades de points, and cardiac arrest when used in combination with other drugs that have the same cardiac toxicities, hallucinations or confusion, and prolonged bleeding when interacting with coumadin.

Dependence appears to be a common problem for all of these drugs except Rozerem.

Dosage wise, it is recommended that starting doses be lowered due to unusual sensitivity to sedative/hypnotic drugs in elderly and/or debilitated patients.

Many off-label treatments are also used clinically, such as antihistamines, certain antipsychotics, and some antidepressants. Many of these carry various significant side effects. None of the available treatment for proposed indication has oral spray formulation.

## 2.4 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor conducted studies under IND #71,290. A pre-IND meeting was held on August 31, 2005. The meeting addressed the product development program including issues of CMC, non-clinical and clinical pharmacology as well as labeling.

For the clinical program, the Division informed the sponsor the following:

- Either strict bioequivalence or a bracketing approach using the approved 5 and 10 mg doses of Ambien with PK values that fall between the approved ranges at all times was required.
- Evaluation of the PK profile of the recommended dose (5mg) for the geriatric population is expected.
- For a claim of acute use for short-term insomnia, a single placebo-controlled study with a lower dose (3-4 mg) of zolpidem lingual spray should be considered, in which both subjective time to falling back to sleep at home and the objective time to fall back to sleep after artificial awakening in the sleep lab are evaluated simultaneously.
- A standard evaluation of the next morning residual drug effects should also be conducted including evaluation of effect on driving behavior, which could be achieved by measure of pre- and post- treatment simulated driving eye-hand coordination

Additionally, the Agency informed the sponsor of the responsibility to look at combinations of drugs, specifically a study of those patients who take chronic medications for sleep maintenance, but with mid-insomnia. For this, our requests are as follows:

- The lingual spray would be used to manage the breakthrough effects.
- Standard measures of next-day residual effects should be included, esp. observations for potential residual effects on driving behavior, which could be evaluated by establishing the subjects' simulated driving eye-hand coordination, then measuring it after study drug treatment.
- This could possibly be approached as open-label safety study in outpatients if a labeling claim for efficacy of sublingual zolpidem in combination is not considered.

Afterwards, on Sept. 22, 2006, the Division communicated some concerns regarding dosage used in non-clinical studies and timing of examine animal oral mucosa, some issues in the CIB, and revisions needed in clinical pharmacology perspective. The sponsor responded to the Division letter on November 7th, 2006 and agreed to all clinical comments. No further related discussion was made between then and NDA submission.

This NDA number was assigned on May 14, 2007. There was no pre-NDA meeting.

## 2.5 Other Relevant Background Information

The sponsor confirmed that drug abuse potential was integrated into the NDA application on Oct. 25, 2007.

On Oct. 30, 2007, the sponsor communicated to the Agency regarding video submission for oral irritation study in rats as part of the final study report; however, it did not satisfy the Agency pharm-tox review (verbal communication with Melissa Banks, Ph.D.). Further clarification was made in the 74-day letter.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality

Generally speaking, the submission quality is acceptable.

## 3.2 Compliance with Good Clinical Practices

Review from DSI is still pending (Please see DSI review for details.)

## 3.3 Financial Disclosures

There is no financial disclosure for the two Principal Investigator, Luis Angles, M.D. (responsible for Study 001) and Evin Henderson Sides, III, M.D. (responsible for Studies 002, 003, and 004) - See Section 5.1 Table of Clinical Studies for details.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

There is no problematic issue from chemistry point of view. For details, please see chemistry review conducted by the Agency Chemistry Reviewer, Shastri Bhamidipati, Ph.D.

## 4.2 Preclinical Pharmacology/Toxicology

Non-clinical PK data are essentially from three studies: MVR-041, MVR-042, MVR-046.

For details, please see pharmacology-toxicology review conducted by the Agency Pharmacology-Toxicology Reviewer Melissa Banks, Ph.D.

## 4.3 Clinical Pharmacology

Below are brief summary of pharmacodynamic and pharmacokinetic information submitted by the sponsor. For detailed review, please see biopharmacology review conducted by the Agency Biopharmaceutical Science Reviewer, Japag Parepally, Ph.D.

### 4.3.1 Pharmacodynamics

Zolpidem induces sleep through GABA-benzodiazepine receptor complexes. In pilot Studies 001 and 2, ZolpiMist was evaluated with Stanford Sleepiness Scales (SSS) and Digital Symbol Substitution Test (DSST) before and after treatments that showed similar sleep effect compared to that of zolpidem; Study 003 and 004, DSST and Visual Analog Scale (VAS) were administered before and after treatments as assessment to show similar effect to that of zolpidem.

### 4.3.2 Pharmacokinetics

After oral administration, zolpidem tablets absorbed rapidly and extensively and then undergoes hepatic first-pass embolism. The oral bioavailability of zolpidem in human is reported as approximately 70%.

The sponsor reports that the first pilot study (001) demonstrated linearity of PK in the dose range of 2.5mg to 10mg; The second pilot study (002) demonstrated that food delays absorption of ZolpiMist; The two definitive PK studies (003 and 004) demonstrated comparable PK parameters to those of zolpidem tablets, in both adults and elderly.

The key PK parameters from definitive PK studies are displayed in the following table.

**Table 2. Comparison of Key Pharmacokinetic Parameters of ZolpiMist in Young Versus Elderly Subjects** (submitted by the sponsor)

| | Mean (SD) | | | |
|---|---|---|---|---|
| Pharmacokinetic Parameter | ZolpiMist, 5 mg, Young ($n = 43$) | Ambien, 5 mg, Young ($n = 43$) | ZolpiMist, 5 mg, Elderly ($n = 24$) | Ambien, 5 mg, Elderly ($n = 24$) |
| $T_{max}$ (min) | 55.0 (36.48) | 52.0 (20.27) | 49.8 (35.95) | 44.4 (21.28) |
| $C_{max}$ (ng/mL) | 114.1 (41.80) | 122.8 (38.39) | 133.7 (51.77) | 127.8 (38.39) |
| $AUC_{0-T}$ (ng·h/mL) | 398.6 (174.09) | 434.8 (169.41) | 457.5 (180.34) | 432.8 (180.75) |
| $AUC_{0-\infty}$ (ng·h/mL) | 432.5 (217.24) | 476.5 (219.21) | 492.9 (213.32) | 465.1 (212.39) |
| $t_{1/2}$ (min) | 163.6 (46.41) | 168.7 (52.46) | 156.2 (47.48) | 153.8 (44.54) |
| Cl/F (L/h) | 15.5 (12.94) | 12.6 (5.46) | 5.96 (2.43) | 6.5 (3.18) |
| Cl/F (L/h/kg) | 0.21 (0.175) | 0.17 (0.079) | 0.08 (0.045) | 0.95 (0.051) |
| Data source: Study NVD-ZOLP-PHL-003, *Table 11.2* and *Table 14.2.1*; Study NVD-ZOLP-PHL-004, *Table 11.2* and *Table 14.2.1*. | | | | |

With regard to metabolism, Zolpidem tartrate is subsequently metabolized mainly thru CYP 3A4; none of its metabolites has pharmacological activities. The sponsor states, "In vitro drug metabolism studies using human liver microsomes indicate that the biotransformation of zolpidem by cytochrome P450 (CYP) isoenzymes mainly involves CYP3A4 isoforms, which appear to account for approximately 60% of zolpidem clearance. Among other isoforms, CYP2C9 is estimated to account for 22% of zolpidem clearance, CYP1A2 for 14%, and CYP2D6 and CYP2C19 for less than 3%."

# 5 Sources of Clinical Data

## 5.1 Table of Clinical Studies

The table below presents the four PK studies submitted for this NDA with a total of 96 subjects.

**Table 3. The Clinical Studies Included in This NDA Application**

| Study Name | Study Title | Study Design | Dosages | Total Subjects |
|---|---|---|---|---|
| NVD-ZOLP-014-04-PHI-001US | A Phase I study of PK of Zolpidem Lingual Spray compared to oral tablet | Dose ranging, open-label, 4-way controlled, 4 dosing with 7±3 days washout period; under fasting condition | 2.5, 5, and 10 mg of zolpimist or 10 mg Ambien | 10 (22-40 year-old) |
| NVD-ZOLP-PHI-002 | A pilot PK study of zolpidem lingual spray compared to oral tablet in healthy male volunteers | Dose ranging, open-label, 5-way crossover, 5 dosing with 7±3 days washout period, in both fed and fasting conditions | 5 and 10 mg of zolpimist or 5 and 10 mg Ambien tablets | 14 (18-45 year-old) |
| NVD-ZOLP-PHI-003 | A definitive PK study of zolpidem lingual spray compared to oral tablet in healthy male and female volunteers | Dose ranging, randomized, open-label, 4-way crossover, 4 dosing with 7±3 days washout period, under fasting condition | 5 and 10 mg zolpimist or 5 and 10 mg Ambien tablets | 48 (18-45 year-old) |
| NVD-ZOLP-PHI-004 | A PK study of zolpidem lingual spray compared to oral tablet in healthy elderly volunteers | Randomized, open-label, 2-way, 2 single treatment with 7±3 days washout period; under fasting condition | 5 mg of Zolpimist or Ambien tablets | 24 (≥65 year-old) |

These studies evaluate PK parameters over the different studied doses and also provide safety and tolerability information about administrations of ZolpiMist in healthy volunteers. Among them, Studies 003 and 004 are the two definitive/pivotal studies.

## 5.2 Review Strategy

Since this application mainly involves open-label PK studies, the clinical review will focus on safety of this NDA, which will be achieved by reviewing all four studies in Section 7 and focusing mainly on death, SAEs, and dropouts because they are all open label studies. I will also briefly summarize the efficacy conclusion from the PD assessments in Section 6, Review of Efficacy and discuss individual studies more in depth in next subsection 5.3.