

Microscopic Observations: Day 15 Euthanasia

Dose	0 4 sprays/day (Water)		0 4 sprays/day (Vehicle)		Low 2 sprays/day (Zolpidem oral spray)		High 4 sprays/day (Zolpidem oral spray)	
	1 1 1 1	1 1 1 1	2 2 2 2	2 2 2 2	3 3 3 3	3 3 3 3	4 4 4 4	4 4 4 4
Animal Number	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M
Day of Euthanasia	0 1 1 1	9 0 1 2 3	2 2 2 2	9 0 1 2	4 5 5 5	9 0 1 2 3	6 7 7 7	9 0 1 2 3
Tissue	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9
-lesion		I		I		I		I
Buccal mucosa, left								
-fibrosis	0 0 0 0	0/5	0 0 0 0	0/4	2 0 0 0	0/5	0 0 0 0	0/5
Gingiva, periodontal								
-inflammation, acute	1 1 1 1	5/5	1 M 1 1	3/3	2 1 1 1	5/5	1 1 1 1	2 5/5
Submandibular lymph node								
-hemorrhage	2 0 0 0	1/5	0 0 0 0	0/4	0 0 0 0	0/5	0 0 0 0	0/5
-necrosis, lymphoid	0 0 0 0	0/5	0 0 0 0	0/4	1 0 0 0	1 2/5	1 0 0 1	2/5
Mesentery, fat								
-granuloma	3 0 0 0	1/5	0 0 0 0	0/4	0 0 0 0	0/5	0 0 0 0	0/5
Stomach, mucosa/submucosa								
-infiltration cellular, eosinophilic	0 0 0 0	2 1/5	0 0 2 0	1/4	0 0 0 0	0/5	0 0 0 0	0/5
Lung								
-inflammation, chronic	* * * *	0/0	* * * 2	1/1	* * * *	0/0	* * * *	0/0
Skin								
-inflammation, subacute, forelimb foot, bilateral	0 0 0 0	0/5	0 0 0 0	0/4	2 0 0 0	1/5	0 0 0 0	0/5
-hyperplasia, epidermal, forelimb foot, bilateral	0 0 0 0	0/5	0 0 0 0	0/4	2 0 0 0	1/5	0 0 0 0	0/5
-hyperplasia, epidermal, forelimb, bilateral	0 0 0 0	0/5	0 0 0 0	0/4	0 0 1 0	1/5	0 0 0 0	0/5

No microscopic lesions were observed in the following tissues: right buccal mucosa, labial junction, tongue, hard palate, soft palate, parotid salivary gland, nasal passages, larynx, trachea, bronchus, and esophagus.

0 = Lesion not observed
 1 = Lesion of minimal severity
 2 = Lesion of mild severity
 3 = Lesion of moderate severity
 4 = Lesion of marked severity

N = Tissue insufficient
 M = Tissue missing
 * = Nonprotocol-specified tissue
 I = Incidence: Number of animals with lesion/number of animals examined

Microscopic Observations: Day 29 Euthanasia

Dose	0 4 sprays/day (Water)		0 4 sprays/day (Vehicle)		Low 2 sprays/day (Zolpidem oral spray)		High 4 sprays/day (Zolpidem oral spray)	
	1 1 1 1	1 1 1 1	2 2 2 2	2 2 2 2	3 3 3 3	3 3 3 3	4 4 4 4	4 4 4 4
Animal Number	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M	M M M M
Day of Euthanasia	1 1 1 1	4 5 6 7 8	3 3 3 3	4 5 6 7 8	5 5 5 5	4 5 6 7 8	7 7 7 7	4 5 6 7 8
Tissue	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9	2 2 2 2	9 9 9 9
-lesion		I		I		I		I
Gingiva								
-inflammation, acute, periodontal	1 1 1 1	5/5	1 1 1 1	5/5	1 1 1 1	5/5	1 1 1 1	2 5/5
-inflammation, subacute	0 0 2 0	1 2/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5
Trachea								
-inflammation, subacute	0 0 0 0	0/5	0 0 0 0	0/5	1 1 0 0	2/5	0 0 0 0	0/5
Parotid salivary gland								
-degeneration	0 1 0 0	1/5	0 0 0 0	0/5	0 0 0 1	1/5	0 0 0 0	0/5
Skin								
-hyperplasia, epidermal, abdominal	0 0 0 0	0/5	1 0 0 0	1/5	0 0 0 0	0/5	0 0 0 0	0/5
-hyperplasia, epidermal, forelimb foot, bilateral	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	1 0 0 0	1/5
-hyperplasia, epidermal, forelimb foot, right	0 0 0 0	0/5	0 0 0 0	0/5	0 0 2 0	1/5	0 0 0 0	0/5
-hyperplasia, epidermal, forelimb, bilateral	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 2 0	1/5
-hyperplasia, epidermal, tail	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 1	1/5
-hyperkeratosis, abdominal	0 0 0 0	0/5	1 0 0 0	1/5	0 0 0 0	0/5	0 0 0 0	0/5
-hyperkeratosis, forelimb foot, bilateral	0 0 0 0	0/5	1 0 0 0	1/5	0 0 0 0	0/5	1 0 0 0	1/5
-hyperkeratosis, forelimb, bilateral	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 2 0	1/5
-hyperkeratosis, tail	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 2 0	1/5
-parakeratosis, forelimb foot, right	0 0 0 0	0/5	0 0 0 0	0/5	0 0 1 0	1/5	0 0 0 0	0/5
-inflammation, subacute, forelimb, bilateral	0 0 0 0	0/5	1 0 0 0	1/5	0 0 0 0	0/5	0 0 0 0	0/5
-inflammation, subacute, hindlimb, left	0 0 0 0	0/5	1 0 0 0	1/5	0 0 0 0	0/5	0 0 0 0	0/5
-inflammation, chronic active, forelimb foot, right	0 0 0 0	0/5	0 0 0 0	0/5	0 0 3 0	1/5	0 0 0 0	0/5
-fibrosis, tail	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 0	0/5	0 0 0 1	1/5

No microscopic lesions were observed in the following tissues: left buccal mucosa, right buccal mucosa, labial junction, tongue, hard palate, soft palate, submandibular lymph node, nasal passages, larynx, bronchus, esophagus, and stomach.

0 = Lesion not observed
 1 = Lesion of minimal severity
 2 = Lesion of mild severity
 3 = Lesion of moderate severity
 4 = Lesion of marked severity

N = Tissue insufficient
 M = Tissue missing
 * = Nonprotocol-specified tissue
 I = Incidence: Number of animals with lesion/number of animals examined

Microscopic Observations: Day 43 Euthanasia

Dose	0 4 sprays/day (Water)		0 4 sprays/day (Vehicle)		Low 2 sprays/day (Zolpidem oral spray)		High 4 sprays/day (Zolpidem oral spray)	
	1 1 1 1 1 M M M M M		2 2 2 2 2 M M M M M		3 3 3 3 3 M M M M M		4 4 4 4 4 M M M M M	
Animal Number	1 2 2 2 2 9 0 1 2 3		3 4 4 4 4 9 0 1 2 3		5 6 6 6 6 9 0 1 2 3		7 8 8 8 8 9 0 1 2 3	
Day of Euthanasia	4 4 4 4 4 3 3 3 3 3	I	4 4 4 4 4 3 3 3 3 3	I	4 4 4 4 4 3 3 3 3 3	I	4 4 4 4 4 3 3 3 3 3	I
Tissue								
-lesion								
Buccal mucosa, left								
-inflammation, acute	0 0 0 0 0	0/5	0 0 0 0 0	0/5	2 0 0 0 0	1/5	0 0 0 0 0	0/5
-inflammation, subacute	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 1 0 0	1/5
Buccal mucosa, right								
-inflammation, subacute	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 0 1 0	1/5
Gingiva								
-inflammation, acute, periodontal	1 1 1 3 1	5/5	2 1 2 1 1	5/5	2 1 2 1 3	5/5	2 1 1 1 2	5/5
-inflammation, subacute	0 0 0 1 0	1/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5
-infiltration, cellular, eosinophilic	0 2 0 0 0	1/5	0 0 0 0 0	0/5	0 0 0 1 0	1/5	0 0 0 0 0	0/5
Soft palate								
-inflammation, subacute	0 1 0 0 0	1/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5
Stomach								
-infiltration, cellular, eosinophilic	0 0 0 0 0	0/5	0 0 2 0 0	1/5	0 0 0 0 0	0/5	0 0 0 0 0	0/5
Skin								
-hyperplasia, epidermal, forelimb, bilateral	0 0 0 0 0	0/5	0 0 0 0 0	0/5	2 0 0 0 0	1/5	0 0 0 0 0	0/5
-hyperkeratosis, forelimb, bilateral	0 0 0 0 0	0/5	0 0 0 0 0	0/5	2 0 0 0 0	1/5	0 1 0 0 0	1/5
-parakeratosis, forelimb, bilateral	0 0 0 0 0	0/5	0 0 0 0 0	0/5	1 0 0 0 0	1/5	0 0 0 0 0	0/5

No microscopic lesions were observed in the following tissues: labial junction, tongue, hard palate, parotid salivary gland, submandibular lymph node, nasal passages, larynx, trachea, bronchus, and esophagus.

- 0 = Lesion not observed
- 1 = Lesion of minimal severity
- 2 = Lesion of mild severity
- 3 = Lesion of moderate severity
- 4 = Lesion of marked severity
- N = Tissue insufficient
- M = Tissue missing
- * = Nonprotocol-specified tissue
- I = Incidence: Number of animals with lesion/number of animals examined

Plasma exposures were variable, although the data generally demonstrated that animals had been exposed to drug. Unfortunately, water and vehicle treated animals also showed evidence of drug exposures; however, the levels were generally low (\leq levels demonstrated 24 hr postdose in LD and HD treated animals). The sponsor attempted to investigate the source of the dose contamination, but was unable to determine the source of the exposures (pgs 289-290 of the report). **See the sponsor's summary tables below.**

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Table 5

28-Day Oral Irritation Study in Sprague Dawley Rats

Summary of Plasma Concentrations of Zolpidem Oral Spray (ng/mL): Recovery Group

Day	Plasma Concentration (ng/mL)			
	Mean ± SD			
	Group 1	Group 2	Group 3	Group 4
1 ^a	0.00 ± 0.00	5.34 ± 5.00	174 ± 123	334 ± 222
15 ^b	0.00 ± 0.00	0.00 ± 0.00	102 ± 42.0	461 ± 311
28 ^b	1.90 ± 1.03	0.75 ± 0.55	170 ± 99.6	1065 ± 523
43 ^b	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

^a Blood collected 60 minutes postdose.

^b Blood collected approximately 24 hours postdose.

For calculations of mean values, NPD was reported as "0"; BQL was reported as half the BQL value given (0.5 ng/mL).

Nominal Dose:

Group 1 – 4 sprays/day (Water)

Group 3 – 2 sprays/day (Zolpidem oral spray)

Group 2 – 4 sprays/day (Vehicle)

Group 4 – 4 sprays/day (Zolpidem oral spray)

Table 5

28-Day Oral Irritation Study in Sprague Dawley Rats

Summary of Plasma Concentrations of Zolpidem Oral Spray (ng/mL)

Day of Euthanasia	Plasma Concentration (ng/mL)			
	Mean ± SD			
	Group 1	Group 2	Group 3	Group 4
5 ^a	0.77 ± 0.85	0.84 ± 0.78	3.82 ± 1.49	6.42 ± 3.41
15 ^b	0.00 ± 0.00	0.00 ± 0.00	0.77 ± 0.37	1.27 ± 0.53
28 ^b	0.90 ± 0.89	1.63 ± 1.55	3.81 ± 1.72	4.00 ± 1.66

^a Blood collected 60 minutes postdose.

^b Blood collected approximately 24 hours postdose.

For calculations of mean values, NPD was reported as "0"; BQL was reported as half the BQL value given (0.5 ng/mL).

Nominal Dose:

Group 1 – 4 sprays/day (Water)

Group 3 – 2 sprays/day (Zolpidem oral spray)

Group 2 – 4 sprays/day (Vehicle)

Group 4 – 4 sprays/day (Zolpidem oral spray)

Conclusions:

It is unclear why the sponsor chose to perform the assay in only males; however, this would not appear to invalidate the study. In this local toxicity assay, the sponsor provided evidence (albeit limited) to document systemic drug exposures in the animals. Abrasion was only performed once during the study.

The local toxicity assay, as performed, demonstrates some irritancy potential of the zolpidem tartrate formulation. Notably, the product has a very low pH (~2; pH of the vehicle used was 1.1). Alopecia, sores and/or ulcers on different sites of the body, and scabs were observed; it is plausible that grooming might have spread the vehicle or test article to the different areas of the body (forefeet, forelimbs, hindlimbs, abdomen and/or chest) where the findings were noted. Mucosal observations indicated some potential for

irritation, and possibly very slightly delayed healing. Erythema at the abrasion site was observed across groups on days 1-4 and might have been slightly more protracted (by about a day) in the LD and HD groups; furthermore, erythema at the abrasion site was sporadically observed in a few zolpidem-treated animals after the initial healing period. Rough lips were observed in vehicle- and zolpidem-treated animals. Generally, histological assessment showed signs of mild irritancy and inflammatory reactions. Early in the study (day 5), signs of minimal-mild inflammation and/or damage were generally observed in the abraded buccal mucosa, periodontal gingiva, labial junction, tongue, larynx and submandibular lymph node. At longer durations, microscopic evaluations demonstrated few remaining abraded buccal mucosa findings (on day 15), but minimal-moderate acute inflammation of the periodontal gingiva and occasional minimal-mild lymphoid necrosis of the submandibular lymph node remained; sporadic findings of possible relevance included mild chronic inflammation of the lung (1 vehicle control animal) and subacute inflammation of the trachea (2 LD). Inflammation, epidermal hyperplasia, hyperkeratosis and fibrosis of varying skin sites were occasionally observed in vehicle, LD and HD animals. The findings appeared to show increased incidence and severity in drug-treated animals on D29, which suggested a drug relationship; regardless, these findings bear relevance to the overall burden of toxicity of the intended product because the toxicities appear result from the highly acidic vehicle, in addition to the drug substance itself.

Overall, evidence of mild irritancy potential for oral mucosae & skin was suggested for zolpidem-treated and vehicle-treated animals; overall, the drug-treated groups demonstrated slightly more potential than the vehicle-treated animals. Clinical signs and histology (e.g., skin sores with minimal-mild histological findings) also suggest that contact with skin and eyes should be avoided. There was a suggestion of a very slight delay in wound healing (~1 day difference). The death of a vehicle control animal (anesthetized during the procedure) due to presumed respiratory distress may suggest that inhalation should be avoided.

2.6.6.8 Special toxicology studies

N/A

2.6.6.9 Discussion and Conclusions

N/A

2.6.6.10 Tables and Figures

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The sponsor's application for ZolpiMist™ zolpidem tartrate oral spray primarily relies on the previous findings of safety for Ambien® (zolpidem tartrate; NDA 19-908), pertinent studies from the public literature and extensive clinical experience with zolpidem. No additional general toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity or abuse liability studies were conducted.

To support the safety of the oral spray formulation, NovaDel conducted two 1-month, repeat-dose, oral irritation studies in rats using zolpidem oral spray formulations to characterize effects on oral and respiratory tissues. The first study used an early formulation and supported the initial clinical trials, but was not considered a definitive study by the Division due to a number of inadequacies. The sponsor then conducted a second definitive study using the final commercial formula of ZolpiMist™ to address the deficiencies that the division identified in the first oral irritation study; the study compared the local toxicity of 28-days administration of a water control spray, a vehicle spray, a 10 mg of the ZolpiMist™ spray, or a 20 mg doses of the ZolpiMist™ spray. In the definitive local toxicity study, ZolpiMist™ oral spray demonstrated a mild irritancy potential for oral mucosae and skin. The mild irritancy potential is not surprising, given that the pH of the spray is low (~2); the pH of the vehicle was stated to be 1.1. The water, vehicle and HD (~20 mg zolpidem) groups all received 4 sprays, while the LD group received 2 sprays (~10 mg zolpidem). Alopecia, sores and/or ulcers on different sites of the body, and scabs were observed; it is plausible that grooming might have spread the vehicle or test article to the different areas of the body (forefeet, forelimbs, hindlimbs, abdomen and/or chest) where the findings were sporadically noted. Mucosal observations indicated some potential for irritation, and possibly very slightly delayed healing. Erythema at the abrasion site was observed across groups on days 1-4 and might have been slightly more protracted (by about a day) in the LD and HD groups; furthermore, erythema at the abrasion site was sporadically observed in a few zolpidem-treated animals after the initial healing period. Rough lips were observed in vehicle- and zolpidem-treated animals. Generally, histological assessment showed signs of mild irritancy and inflammatory reactions that seemed exacerbated in the drug-treated and vehicle groups. Early in the study (day 5), signs of minimal-mild inflammation and/or damage were generally observed in the left treated buccal mucosa, periodontal gingival, labial junction, tongue, larynx and submandibular lymph node. At longer durations, microscopic findings on D15 demonstrated few remaining left buccal mucosa findings, but the minimal-moderate acute inflammation of the periodontal gingiva and occasional minimal-mild lymphoid necrosis of the submandibular lymph node remained; sporadic findings of possible relevance included mild chronic inflammation of the lung (1 vehicle control animal) and subacute inflammation of the trachea (2 LD). Inflammation, epidermal hyperplasia, hyperkeratosis and fibrosis of varying skin sites were occasionally observed in vehicle, LD and HD animals; it was difficult to ascertain whether to attribute these somewhat sporadic effects to drug and/or vehicle, but the overall incidence appeared greater in the drug-treated groups.

During the course of development, _____ was identified as the principal degradation product of ZolpiMist™ _____ is a _____ of zolpidem tartrate and is also _____ to zolpidem tartrate. The sponsor determined that the amount of _____ in each 10 mg ZolpiMist™ dose would exceed the threshold dose for qualification (0.5% total daily intake) noted in *FDA Guidance for Industry Q3B(R2): Impurities in New Drug Products*, July 2006. In accordance with the guidance document, NovaDel performed studies to qualify this impurity; specifically, the safety profile of _____ was characterized in: two *in vitro* genotoxicity studies (i.e., *in vitro* bacterial reverse-mutation test and *in vitro* mammalian chromosome-aberration test); a single-dose, acute toxicity study; two 7-day repeat-dose toxicity studies; and a 28-day repeat-dose, toxicity study in rats.

b(4)

b(4)

The maximum amount of _____ in a single clinical daily 10 mg dose of ZolpiMist™ (drug product release specification of _____ yielding a maximum anticipated _____ exposure of _____ does not appear to present a risk to humans at the proposed therapeutic doses of zolpidem tartrate (10 mg). As performed, the *in vitro* genotoxicity assays identified _____ as non-genotoxic. The nonclinical studies to assess the toxicity profile of _____ demonstrated little associated toxicity at levels substantially higher than the maximum anticipated exposure in humans. There were alterations in body weight gains (increased up to 13% in treated males, and decreased 30% in high dose females). At the high dose (250 mg/kg), liver weight was increased, hemoglobin and hematocrit were minimally decreased, and APTT was significantly increased in males. Also at high dose, there was some suggestion of hemorrhage in multiple organs and a **suggestion of exacerbated, possibly "age-related," histologic changes in the heart and kidney.** The NOAEL doses in the definitive 28-day rat study provide at least an approximate _____ safety margin over the clinical daily maximum anticipated _____ exposure that humans will receive (see Table 1, excerpted from the Expert Opinion Report for the Toxicologic Qualification of _____ impurity by _____).

b(4)

b(4)

Table 1: Safety Factors for Clinical _____ Exposure

Study	Sex	NOAEL mg/kg	HED ^a	Max _____ exposure/day	Safety Factor ^b
28-Day Oral Toxicity in Rats	Male				4,838
	Female				24,202

b(4)

a: Human Equivalent Dose (HED) calculated by dividing the NOAEL in rats by the conversion factor of 0.2 according to FDA Guidance *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (2005).
b: Safety factor calculated by dividing the HED by the maximum TIP acid dose in humans.

Unresolved toxicology issues (if any):
There are no unresolved toxicology issues at this time.

Recommendations:
Please see the recommendations in the Executive Summary.

Suggested labeling:
Please see the recommendations in the Executive Summary.

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/s/

Melissa Banks
12/17/2008 05:13:18 PM
PHARMACOLOGIST

Lois Freed
12/17/2008 05:40:36 PM
PHARMACOLOGIST

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MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

Date: December 17, 2008

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-196 (ZolpiMist®; zolpidem tartrate oral spray)

NovaDel Pharma has submitted NDA 22-196, a 505(b)(2) application, for zolpidem tartrate oral spray for short-term treatment of insomnia characterized by difficulties with sleep initiation. In support of this application, the sponsor has provided the following nonclinical studies:

- 1-month repeat-dose oral mucosal irritation studies in rat (2 studies)
- Studies to qualify degradant _____ (present in ZolpiMist at a level of _____)
 - Acute and repeat-dose (two seven-day, 28-day) oral studies in rat
 - Genetic toxicology (Ames test, in vitro chromosomal aberration assay in CHO cells)

b(4)

These studies have been reviewed in detail by Melissa K. Banks, Ph.D. (Pharmacology/Toxicology Review and Evaluation, NDA 22-196, 12/16/08). Dr. Banks has concluded that these data support approval of NDA 22-196. I concur.

Recommended labeling

- Based on labeling recommended by Drs. Banks and Fisher.
- Basis for calculated safety margins:
 - Recommended human dose (RHD) = 10 mg/day of zolpidem tartrate (or
Zolpidem tartrate MW = 764.89
Zolpidem MW = 307.395
ZolpiMist is a 2:1 zolpidem:tartrate salt
- Incorporates wording regarding observations in humans recommended by the MHT.

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Lois Freed
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