

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-196
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 11/21/07
PRODUCT: ZolpiMist™ (zolpidem tartrate) Oral Spray
INTENDED CLINICAL POPULATION: Insomnia
SPONSOR: NovaDel Pharma Inc.
DOCUMENTS REVIEWED: Electronic submissions dated: 11/20/07
6/28/08
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REVIEW DIVISION: Division of Neurology Products
(HFD-120)
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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a Pharmacology / Toxicology perspective, this New Drug Application is approvable.

B. Recommendation for nonclinical studies

There are no recommendations for further nonclinical studies at this time.

C. Recommendations on labeling

The following labeling changes outlined below are recommended at the time of this review. As such, labeling negotiations have not yet occurred and the wording in the final approved label may differ from that which follows.

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✓)
II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

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 open 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 ZolpiMist™ to characterize effects on oral and respiratory tissues. The first study was not considered a definitive study by the Division due to a number of deficiencies. A second definitive study using the final commercial formula of ZolpiMist™ was conducted to address the inadequacies that the division identified in the first oral irritation study; the definitive 1-month local toxicity study compared the effects of a water control, a vehicle control, a nominal 10 mg dose (the MRHD) and a nominal 20 mg dose (2 times the MRHD). This study 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 for ZolpiMist™ and ~1 for vehicle). Clinical, mucosal, and gross pathology observations indicated some potential for irritation, and possibly very slightly delayed healing. Generally, histological assessment of the buccal cavity showed signs of mild irritancy and inflammatory reactions. Additionally, inflammation, epidermal hyperplasia, hyperkeratosis and fibrosis of varying skin sites were occasionally observed in vehicle, LD and HD animals; the findings suggested a drug relationship, but also 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.

During the course of the ZolpiMist™ development program, _____ was identified as the principal degradation product of ZolpiMist™ _____ of zolpidem tartrate and is also a _____ zolpidem tartrate. The sponsor determined that the amount of _____ in each 10 mg ZolpiMist™ daily 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; therefore, studies to qualify this impurity were conducted (i.e., two *in vitro* genotoxicity studies [a bacterial reverse mutation test and an *in vitro* mammalian chromosome aberration test], a single-dose acute toxicity study in rats, two 7-day repeat-dose toxicity studies in rats, and a 28-day repeat-dose toxicity study in rats). The proposed maximum amount of _____ in a daily 10 mg dose of ZolpiMist™ (drug product release specification of NMT _____ yielding a maximum anticipated _____ exposure of _____ µg/day) does not appear to present a risk to humans at the proposed/approved therapeutic doses of zolpidem tartrate (10 mg). See the sponsor's Table 1 for safety factors comparing the NOAEL from the 28-day study of the impurity and the maximum exposure resulting from the clinical dose.

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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

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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 TID acid dose in humans.

B. Pharmacologic activity

No new studies characterizing the pharmacology of zolpidem were conducted. Zolpidem has been characterized as an agonist at the benzodiazepine (BZ or ω) binding site on the α -subunit of GABA_A receptors. Zolpidem was shown, *in vitro*, to bind the BZ₁ receptor preferentially, with a high affinity ratio of the α_1/α_5 subunits.

C. Nonclinical safety issues relevant to clinical use

ZolpiMist™ demonstrated mild irritancy potential for mucosae and skin. The spray formulation has a low pH (~ 2). Avoidance of contact with skin and eyes, as well as inhalation, is recommended.

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Relevant INDs/NDAs/DMFs: 171,290

Reference to approved N19-908

Also reference to the following DMFs:

- DMF _____

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Drug class: Sedative/hypnotic, GABA_A agonist

Intended clinical population: Insomnia

Clinical formulation:

Table 2.3.P.1-1. Unit Composition of ZolpiMist

Compound	Reference to Quality Standard	Function	Quantity per Unit		
			% w/w	% w/v	mg/100 µL
Zolpidem Tartrate	Ph. Eur.	Drug substance	_____	5.00	5.00
Artificial Cherry Flavor	In-house				
Benzoic Acid	USP				
Citric Acid, Monohydrate	USP				
Hydrochloric Acid	NF				
Neotame	NF				
Propylene Glycol	USP				
Purified Water	USP				
Total					

Ph. Eur. = European Pharmacopoeia.
 NF = National Formulary.

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Route of administration: Oral spray

Data reliance : Any information or data necessary for approval of N 22-196 that NovaDel does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that NovaDel does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of N 22-196. NovaDel identified Sanofi-Aventis' NDA 19-908, Ambien[®] tablets, as the Reference Listed Drug for this 505(b)(2) application.

Studies reviewed within this submission:
See the sponsor's summary table, below, for reports submitted:

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Table 2.6.1-1. NovaDol's Toxicology Studies for Zolpidem and [redacted] [redacted]							Relationship to Maximum Human Dose of 12.5 mg in a [redacted]	GLP
Type of Study	Study Number/ NDA Section	Lot Number	Species	Route	Duration of Treatment	Dose Groups		
Zolpidem								
Repeat-Dose Oral Mucosal Irritation and Upper Respiratory Tract Toxicity (Using a Placebo Formulation of Zolpidem)	MB-06-14381.15 Section 4.1.3.2	S-1403-079	Rat	Oral (spray)	30 days (routed to as 1 month)	2 sprays of vehicle or 2 sprays of Zolpidem (20 mg/day)		Yes
Repeat-Dose Oral Irritation (Using the Final Clinical Commercial Formulation of Zolpidem)	12230.01.01 Section 4.1.3.2	07C03 200703300C	Rat	Oral (spray)	28 days (routed to as 1 month)	4 sprays of water 4 sprays of vehicle 2 sprays of Zolpidem (20 mg/day) 4 sprays of Zolpidem (20 mg/day)		Yes
Single-Dose	12230.01.01 ^d Section 4.1.3.7.6	051018 (B44-L-1) ^e	Rat	Oral	1 day	0, 25, 100, 250, and 500 mg/kg		No
Repeat-Dose	12230.01.01 ^d Section 4.1.3.7.6	051018 (B44-L-1) ^e	Rat	Oral	7 days (4-day minimum)	0, 25, 100, and 500 mg/kg		Yes
Repeat-Dose	12230.01.01 ^d Section 4.1.3.7.6	051018 (B44-L-1) ^e	Rat	Oral	7 days	0, 25, 100, and 500 mg/kg		Yes
Repeat-Dose	12230.01.01 ^d Section 4.1.3.7.6	051018 (B44-L-1) ^e	Rat	Oral	28 days	0, 12.5, 50, and 250 mg/kg		Yes
Genotoxicity Ames Assay	JC902C-384-BZZ Section 4.1.3.7.8	051018 (B44-L-1) ^e	<i>S. typhimurium</i> <i>E. coli</i>	In vivo	48-72 h incubation	1.5-5000 µg/plate		Yes
Genotoxicity Chromosome Aberration	JC902C-381-BTE Section 4.1.3.7.8	051018 (B44-L-1) ^e	Chinese hamster ovary cells	In vivo	4 h incubation 20 h incubation	07.5-2500 µg/mL 07.5-2500 µg/mL	NA	Yes
<p>^a Intraspecies comparisons are based on body surface area. The maximum human dose of zolpidem is 12.5 mg/day.</p> <p>^b [redacted] prepared an expert opinion report for the Zolpidem oral irritation studies.</p> <p>^c [redacted] Senior Committee. [redacted] prepared an expert opinion report for the [redacted] toxicology studies.</p> <p>^d Expert Opinion Report</p> <p>^e In Study 12230.01.01, 051018 contains the information for Studies 12230.01.01, 12230.01.02, 12230.01.03, 12230.01.04, 12230.01.05, 12230.01.06, 12230.01.07, 12230.01.08, 12230.01.09, 12230.01.10, 12230.01.11, 12230.01.12, 12230.01.13, 12230.01.14, 12230.01.15, 12230.01.16, 12230.01.17, 12230.01.18, 12230.01.19, 12230.01.20, 12230.01.21, 12230.01.22, 12230.01.23, 12230.01.24, 12230.01.25, 12230.01.26, 12230.01.27, 12230.01.28, 12230.01.29, 12230.01.30, 12230.01.31, 12230.01.32, 12230.01.33, 12230.01.34, 12230.01.35, 12230.01.36, 12230.01.37, 12230.01.38, 12230.01.39, 12230.01.40, 12230.01.41, 12230.01.42, 12230.01.43, 12230.01.44, 12230.01.45, 12230.01.46, 12230.01.47, 12230.01.48, 12230.01.49, 12230.01.50, 12230.01.51, 12230.01.52, 12230.01.53, 12230.01.54, 12230.01.55, 12230.01.56, 12230.01.57, 12230.01.58, 12230.01.59, 12230.01.60, 12230.01.61, 12230.01.62, 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