CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number:	N21-997
Submission Number/code:	N000
CDER Stamp Date:	5/14/08
PDUFA Date:	3/14/09
Product:	zolpidem tartrate sublingual tablet
Indication:	Treatment of insomnia
Applicant:	Orexo AB
Review Division:	HFD-120; Division of Neurology Products
Reviewer:	Melissa K. Banks, Ph.D.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Cathleen Michaloski, BSN, MPH

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TABLE OF CONTENTS

1. Executive Summary

1.1. Recommendations

1.1.1. Approvability

This 505(b)(2) application is approvable from a Pharmacology/Toxicology perspective.

1.1.2. Additional nonclinical comments

No additional pharmacology or toxicology studies were required for this application for a sublingual tablet formulation of zolpidem tartrate, an approved drug. The need for an adequate local irritation study was mitigated by the sponsor's submission of 1) data from clinical evaluation of local tissues and 2) evidence (i.e., PK) demonstrating that the drug does not appear to be substantially absorbed across the oral mucosae. An older local irritation assay, as conducted, demonstrated some potential for mild irritation.

1.1.3. Labeling

[Note: These recommendations reflect the reviewer's opinion, but have not been subject to internal discussion or external negotiation and may not reflect final labeling.]

HIGHLIGHTS
USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm. (8.1)
- Nursing mothers: Infant exposure via breast milk. (8.3)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in of TRADENAME in pregnant women. TRADENAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born to mothers taking sedative-hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 10 mg/day (8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg (≈5, 24, and 120 times the MRHD on a mg/m^2 basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification were observed at all but the low dose, which is 5 times the MRHD on a mg/m^2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg (≈2.5, 10, and 40 times the MRHD on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification were seen at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is ≈10 times the MRHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg (≈5, 24, and 120 times the MRHD on a mg/m^2 basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the low dose, which is ≈5 times the MRHD on a mg/m^2 basis.

8.2 Labor and delivery

TRADENAME has no established use in labor and delivery. [see Pregnancy(8.1)].

8.3 Nursing mothers

Zolpidem is excreted into human milk. Studies in lactating mothers indicate that the $t_{1/2}$ of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hours). The effect of zolpidem on the nursing infant is not known.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. In mice, these doses are ≈2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m^2 basis. In rats, these doses are ≈5, 20, and 100 times the MRHD on a mg/m^2 basis. No evidence of carcinogenic potential was observed

in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Mutagenesis: Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

Impairment of fertility: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg or ≈5, 24, and 120 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. The no-effect dose for these findings is ≈24 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

1.2. Evaluation and discussion of nonclinical findings affecting regulatory decision

1.2.1. Basis of Recommendation

The product TRADENAME is a new sublingual oral formulation of approved product zolpidem (Ambien®, N19-908). The product does not incorporate novel excipients. Furthermore, TRADENAME was deemed not to be substantially absorbed across the oral mucosae and did not cause notable adverse effects during detailed clinical examinations during a repeated-dose trial (OX22-007); therefore, additional local toxicity data (to supplement a local toxicity assay evaluated as inadequate) were not required.

1.2.2. Clinical Implication

n/a

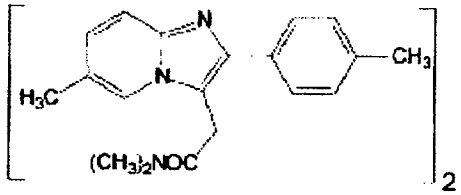
2. Drug Information

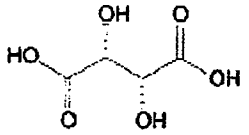
2.1. Drug:

2.1.1. Pharmacological class	Sedative/hypnotic
2.1.2. CAS registry number (optional):	99294-93-6
2.1.3. Generic name:	zolpidem tartrate
2.1.4. Code name:	OX22
2.1.5. Chemical name	N,N,6-trimethyl-2-p-tolylimidazo(1,2-a)pyridine-3-acetamide L-(+)-tartrate (2:1) OR bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate

2.1.6. Molecular formula/molecular weight: $C_{42}H_{48}N_6O_8$; 764.9

2.1.7. Structure:





2.2. Clinical formulation:

2.2.1. Drug formulation:

OX22 is a zolpidem tartrate sublingual tablet; to-be-marketed strengths are 5 and 10 mg. The composition is delineated in sponsor's Table 6, following.

Table 6: Final Commercial Product (FCP) - Composition of Zolpidem tartrate sublingual tablets 5 and 10 mg

Components	Each 5 mg tablet contains (mg)	Each 10 mg tablet contains (mg)	Function	Reference to quality standard
Zolpidem tartrate,	5.00	10.0	Drug substance	Ph. Eur.
Mannitol				USP, Ph. Eur.
Silicified microcrystalline cellulose[3]				USP, Ph. Eur.
Silicon dioxide, colloidal				USP, Ph. Eur.
Croscarmellose sodium				USP, Ph. Eur.
Saccharin sodium				USP, Ph. Eur.
Magnesium stearate				USP, Ph. Eur.
Tablet weight	**120 mg**	**130 mg**		

b(4)

[3] Mixture of the pharmacopoeial excipients silicon dioxide and microcrystalline cellulose.

The following summary is paraphrased from the sponsor's submission:
The zolpidem tartrate sublingual tablet (OX-22) was designed as a convenient, rapidly disintegrating tablet with mucoadhesive properties for sublingual administration for treatment of short-term insomnia in adults and the geriatric population. The development of the drug product is based on a patented interactive (ordered) mixing principle with selected excipients which provide the desired product characteristics. OX22 tablets are designed to disintegrate rapidly under the tongue upon contact with saliva thus eliminating the need for swallowing an intact tablet or taking the tablet with water as compared to existing oral zolpidem products in the market.

2.2.2. Comments on excipients:
The excipients appear to be standard, pharmacopoeial ingredients, and in accordance with other oral and/or ODT formulations. There are no novel excipients in the formulation.

2.2.3. Comments on impurities/degradants:
The sponsor identified impurities of potential concern, (see sponsor's Table 2). Orexo specifications are below the identification and qualification thresholds of the ICH Q3A (Feb 2003) guideline, see sponsor's Tables 3 and 4. Additionally, evaluation of zolpidem tartrate and its synthetic process for structural alerts related to genotoxicity (c.f., ICH S2B [Nov 1997]) found none. b(4)

Table 2: Names and structures of identified impurities and degradation products.

b(4)

Table 3: Lower level of detection and lower level of quantification determined for the HPLC method for related substances according to Ph. Eur.

LLQ - Lower Level of Quantification	LLD - Lower Level of Detection	ICH Q3A Identification threshold	ICH Q3A Qualification threshold
		0.10 %	0.15 %

b(4)

Table 4: Impurity and degradation product limits in specifications according to Orexo compared to ICH thresholds.

Impurity	specification	Orexo specification	ICH Q3A Identification threshold	ICH Q3A Qualification threshold
	NMT	%	0.10 %	0.15 %
	NMT	%	0.10 %	0.15 %
Total	NMT			

b(4)

2.3 Proposed clinical population and dosing regimen:

Indication:
Treatment of short-term insomnia characterized by difficulties with sleep initiation

Dosing Regimen (sponsor's proposed regimen, based on clinical studies of TRADENAME and the current Ambien® label):

The recommended daily dose for OX22 for adults is 10 mg immediately before bedtime, and only when they are able to stay in bed a full night (7-8 hours) before being active again. The total daily dose should not exceed 10 mg. OX22 should be placed under the tongue, where it will rapidly

disintegrate. The tablet should be taken without water and should not be swallowed. OX22 should not be administered with or immediately after a meal. An initial 5 mg dose is recommended in elderly or debilitated patients because elderly or debilitated patients may be especially sensitive to the effects of zolpidem.

2.4. Regulatory background & Interactions with the Agency:

The NDA was initially submitted 1/12/06, but the Division refused to file (RTF) the application at that time due to a number of deficiencies, none involving the nonclinical data. The primary nonclinical issue, discussed with the sponsor at a meeting held 5/1/06, was the need for assessment of local irritation. The Division noted that the pharmacokinetic (PK) differences between the approved zolpidem formulations and the sponsor's ODT formulation would be important in determining what local toxicity assessment(s) would be required, and specifically whether a repeat nonclinical local toxicity assay would be required. The Division stated that the adequacy of the assessment of local toxicity would be a review issue, but if the PK for the sponsor's ODT formulation were similar to Ambien IR, then it would be assumed that OX22 is not absorbed transmucosally. Local irritation was assessed in clinical trials.

Relevant INDs, NDAs, and/or DMFs:

Reference Listed Drug product: Ambien®, NDA #19-908 (Sanofi-Aventis)

3. *Studies submitted within this submission:*

3.1. Studies reviewed within this submission

Table 1

							Test article: OX22	
Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Compliance	Testing Facility	StudyNumber	Location in dossier
Oral irritation	Hamster Syrian	To the cheek pouch	28 days	5, 10	Yes	[redacted]	10797/01	Module 4.2.3.6

b(4)

3.2. Studies not reviewed within this submission: n/a

Notes: SD= single dose, LD= low dose, MD= medium dose, HD= high dose, M= male, F= female, D= day, Wk= week, Mo= month; [ss]= statistically significant, [nss]=not statistically significant, gp=group, conc=concentration; trtmt=treatment

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

10. Special toxicology studies:

Study title: OX22- Oral irritation test in the Syrian Hamster

Key study findings:

Inadequate study due to a number of methodological deficits

Overall, there appeared to be some evidence of treatment- and possibly dose-related irritancy (e.g., erythema)

Study no.: Study 59259
Sponsor Rpt 10797/01

Study report location: Electronic submission

Conducting laboratory and location:

b(4)

Date of study initiation: animal arrival- 6/9/05
Experimental- 6/21/05

GLP compliance: Yes, OECD GLP

QA statement: Yes

Drug, lot #, and % purity: OX 22,0 mg (placebo) - Batch No RF1303P
OX 22,5 mg - Batch No RF1304
OX 22, 10 mg - Batch No RF1308
Expiry: All batches, July 2006

Methods -

Species/strain: Syrian hamsters, SPF

b(4)

Weight: 83-115g

Dose & Number/sex/group (main study): see sponsor's table below

Animal No	Group No	Sex	Treatment	Colour code
1 - 6	1	Male	OX 22 Placebo sublingual tablet	White
7 - 12		Female		
13 - 18	2	Male	OX 22 5 mg sublingual tablet	Blue
19 - 24		Female		
25 - 30	3	Male	OX 22 10 mg sublingual tablet	Green
31 - 36		Female		

Route: PO, sublingual tablet

Formulation/vehicle: Clinical Formulation II (Qualitatively but not quantitatively the same as the final proposed commercial product, in terms of excipients, see sponsor's Table 1, next page)

Dosing solution analyses: n/a, provided as tablets ready to use

Unique study design or methodology: Food: pelleted *ad lib.*
Water: *ad lib.* bottles "with domestic quality water acidified to pH 2.5 with HCl acid in order to prevent microbial growth"

Table 1: Formulations of Zolpidem tartrate sublingual tablets used in clinical and toxicology studies

Components	Function	Formulation I (mg)	Formulation II (mg)	Final Commercial Product (mg)
Zolpidem tartrate,	Drug substance	5.00/10.0		
Zolpidem tartrate	Drug substance	-	10.0	10.0
Mannitol				
Silicon dioxide, colloidal				
Silicified microcrystalline cellulose				
Croscarmellose sodium				
Saccharin sodium				
Magnesium stearate				
Total weight		**80.0 mg**	**105 mg**	**130 mg**
Formulation(s) used for clinical programs				
		OX22-001		
		OX22-002		
		OX22-004[1]	OX22-004	
			OX22-005	
			OX22-006	
				OX22-007
			OX22-008	OX22-008

b(4)

Details of the compositions of these formulations are provided in section 3.2.P.2.2.

[1] Only Zolpidem tartrate sublingual tablet 10 mg was studied.

Brief method summary:
The study was conducted according to CPMP (Committee for Proprietary Medicinal Products) Guideline CPMP/SWP/2145/00, March 2001 Note for Guidance on nonclinical local tolerance testing of medicinal products. Eight days prior to start of treatment, the cheek pouches were rinsed with physiological saline solution and the animals were fitted with a 4 mm collar around the neck (in order to permit normal feeding and respiration but to prevent the storing of food in the pouches). Prior to start of treatment, animals were weighed at intervals and the check pouches were examined to ensure that they were empty. At the initiation of treatment (Day 1), the collar was removed and the cheek pouches were rinsed with physiological saline solution. An otoscope was used to examine for any abnormalities prior to treatment.

The appropriate test item was administered in the left pouch of each animal in the respective groups. Tablets were placed in the left cheek pouch using curved metal forceps, with ends covered in a short length of plastic tubing. No sample was placed in the right cheek pouch, which served as individual control. After treatment a new collar was placed on the animal and the animal was returned to its cage. This procedure took place once daily for 28 consecutive days.

Observations times and results:

Mortality & Clinical signs: *All visible signs were recorded during the study period.*
All animals survived to termination of the study. On Days 8 and 9, one HD animal had swollen cheeks. On Day 9, two controls had swollen cheeks; one of these animals showed the same sign on Day 10. No other adverse clinical findings were observed. These findings were not considered related to the test article or the tablet formulation itself, as they were seen in drug-treated and control animals and both cheeks of the affected animals were involved.

Body weights: *on Day 1, and weekly thereafter, to termination*
No drug-related changes in body weight gain were observed. See the sponsor's summary tables below.

OX 22

Oral irritation test in the Syrian Hamster

Body weight and body weight gain (g)

Group mean values - Day of arrival to day 29

Males

GROUP	ON ARRIVAL			DAY -8			DAY 1			DAY 8		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
1	90.3	4.4	6	99.3	5.5	6	111.2	5.1	6	117.5	5.8	6
2	89.5	2.3	6	96.0	3.6	6	106.0	6.5	6	114.3	9.5	6
3	96.5	6.0	6	104.8	3.7	6	116.7	6.6	6	124.3	7.1	6

GROUP	DAY 15			DAY 22			DAY 29			BODY WT GAIN 1-29		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
1	126.0	10.7	6	126.7	10.0	6	130.7	10.3	6	19.5	3.9	6
2	120.8	11.1	6	124.0	11.4	6	128.7	12.8	6	23.7	7.6	6
3	131.5	10.3	6	138.2	10.0	6	145.0	8.9	6	28.3	6.1	6

OX 22

Oral irritation test in the Syrian Hamster

Body weight and body weight gain (g)

Group mean values - Day of arrival to day 29

Females

GROUP	ON ARRIVAL			DAY -8			DAY 1			DAY 8		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
1	93.8	3.9	6	97.5	4.8	6	111.3	6.4	6	119.3	8.0	6
2	97.3	5.9	6	100.8	3.3	6	112.8	6.5	6	119.0	9.2	6
3	97.2	8.4	6	99.3	6.7	6	112.3	8.2	6	117.8	4.6	6

GROUP	DAY 15			DAY 22			DAY 29			BODY WT GAIN 1-29		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
1	123.7	12.1	6	128.7	13.7	6	133.5	12.6	6	22.2	6.6	6
2	127.8	11.1	6	129.8	11.4	6	132.8	11.3	6	20.0	7.1	6
3	127.2	6.3	6	130.5	6.7	6	134.7	7.5	6	22.3	11.6	6

Gross pathology:

Daily-

The pouches were examined macroscopically using an otoscope immediately prior to the daily treatment as well as at termination of the study. The scores were recorded as follows (excerpted from the sponsor's submission):

The appearance of the cheek pouches for each animal was described, and at each time interval the pouch surface reactions in each animal were graded as follows:

Reaction	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

During the daily observations, no erythema to very slight erythema (score 1) was recorded at most observations of the left cheek pouch (test site) in all 3 groups. On a total of 8 occasions, well-defined erythema (score 2) was observed in 5 HD animals.

For the right cheek pouch (control site), no erythema was recorded for most of the observations in all 3 groups. On 5-7 occasions in each group, very slight erythema (score 1) was observed in 4-5 animals in each of the 3 groups.

Necropsy-

The data were summarized separately for males and females. The scores for macroscopic evaluation of all left test cheek pouches in each group were added and divided by the number of observations to obtain a group average. The same evaluation was carried out for the right cheek pouches (controls). The average score for the control site was subtracted from the average score of the test site for each group to obtain the macroscopic score for the three different groups.

At necropsy, the following frequencies of the reactions (scores 0-1) were recorded (from the sponsor's submission):

Left cheek pouch (test site)

Individual score	Number of male animals showing reactions			Number of female animals showing reactions		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Score 0	5	3	4	3	3	2
Score 1	1	3	2	3	3	4

(The macroscopic findings at necropsy is also presented as pouch surface reactions on Day 29 in Appendix III)

Right cheek pouch (control site)

Individual score	Number of male animals showing reactions			Number of female animals showing reactions		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Score 0	5	5	5	5	6	5
Score 1	1	1	1	1	0	1

(The macroscopic findings at necropsy is also presented as pouch surface reactions on Day 29 in Appendix III)

These scores were used to calculate an average score for the test item (per group; from the sponsor's submission):

	Male animals			Female animals		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Average score	0.00	0.33	0.17	0.33	0.50	0.50

Histopathology:

Adequate Battery: Yes, for a local irritation assay

Peer review: No

The cheek pouches were isolated and fixed in 4% neutral phosphate buffered formaldehyde. After fixation, two samples of the oral tissue were embedded in paraffin, cut at a nominal thickness of 5 µm, stained with H&E and examined under a light microscope. The microscopic findings were graded according to the following grading system, below.

Reaction	Numerical grading
1. Epithelium	
Normal, intact	0
Cell degeneration or flatting	1
Metaplasia	2
Focal erosion	3
Generalised erosion	4
2. Leukocyte infiltration (per high power field)	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4
3. Vascular congestion	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked, with disruption of vessels	4
4. Oedema	
Absent	0
Minimal	1
Mild	2
Moderate	3
Marked	4

See the sponsor's histologic data, below:

PATHOLOGY REPORT — PAGE : 2/ 23
SUMMARY TABLES — PROJECT : 10518/01

TEST ARTICLE : OX 22 — PATHOL. NO.: 59259 GN
TEST SYSTEM : HAMSTER, 28 days, Cheek pouch — DATE : 02-SEP-05
SPONSOR : Orexo AB — PathData@System V6.2a2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: MO

DOSE GROUP:	1		2		3	
SEX :	M	F	M	F	M	F
NO.ANIMALS:	6	6	6	6	6	6
LEFT CHEEK POUCH :	6	6	6	6	6	6
- Leucocyte infiltrat.:	-	-	1	-	-	-
Grade 1:	-	-	1	-	-	-
- Vascular congestion :	-	-	-	1	-	-
Grade 1:	-	-	-	1	-	-
RIGHT CHEEK POUCH :	6	6	6	6	6	6
- Epithelium :	-	-	-	1	-	-
Grade 1:	-	-	-	1	-	-
- Leucocyte infiltrat.:	-	-	-	2	-	1
Grade 1:	-	-	-	2	-	1

To calculate summary scores for evaluation, the scores for the individual microscopic evaluations for all the test cheek pouches were added and divided by the number of observations to obtain a group average. The same evaluation was performed for the control cheek pouches. The maximum score was 16. The average control cheek pouch (right) score was subtracted from the average test cheek pouch (left) score to obtain the Irritation Index (IrI) for the group. The IrI for each group was classified according to the five response categories given in the table below (from the sponsor's submission):

Irritation Index	
0	None
1 to 4	Minimal
5 to 8	Mild
9 to 11	Moderate
12 to 16	Severe

The sponsor reported no histologic evidence of irritation as calculated, for any group. That is, in no group did the IrI for either the treated or untreated cheek pouch achieve an IrI of 1. The calculated IrIs for placebo, LD and HD were 0 (0 – 0 for M & F), 0.17 to 0 (0.17 - 0 for M, 0.17 – 0.5 for F), and 0 (0-0 for M and 0 – 0.17 for F).

11. Overall integrated summary and safety evaluation:
Please see the Executive Summary.

As a 505(b)(2) application for a zolpidem tartrate sublingual formulation, the sponsor relied on the Agency's findings of safety for Ambien® (RLD) for most of the nonclinical data. Only a nonclinical local toxicity study was initially requested to address the potential change in route of administration (i.e., transmucosal vs. oral), with assessment

of the local tissue(s) that could be affected by this product. The local irritation study provided was inadequate due to a number of methodological deficiencies; however, some evidence of minimal irritation was observed (as measured by incidences of increased erythema severity scores during daily gross observations, but without confirmation at necropsy or histologic corroboration). Abrasion of the mucosae was not performed, so evaluation of the effect of the formulation on wound healing was not possible. The need for a repeat, adequate local toxicity study was mitigated by the sponsor's submission of 1) data from clinical evaluation of local tissues and 2) evidence (i.e., PK) to demonstrate that the drug does not appear to be substantially absorbed across the oral mucosae. Discussions with the clinical and clinical pharmacology reviewers (Drs. Kasim and Parepally) indicated that these data were sufficient; therefore, additional nonclinical local toxicity testing would not be needed.

12. Appendix/Attachments: n/a

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/s/

Melissa Banks
3/11/2009 01:17:16 PM
PHARMACOLOGIST

Lois Freed
3/12/2009 04:20:29 PM
PHARMACOLOGIST
I concur.