# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-774**

# PHARMACOLOGY REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

## SECONDARY PHARMACOLOGY TOXICOLOGY REVIEW

| | |
|---|---|
| **Date:** | April 1, 2005 |
| **To:** | Bob Rappaport, M.D.<br>Division Director, DACCADP (HFD-170) |
| **cc.** | Rigoberto Roca, M.D.<br>Deputy Division Director, DACCADP |
| **From:** | R. Daniel Mellon, Ph.D.<br>Supervisory Pharmacologist, DACCADP |
| **Subject:** | Supervisory Pharmacology/Toxicology Review of NDA 21-774 (Ambien CR [Zolpidem tartrate Extended-release tablets]) |
| **Date of Submission:** | June 8, 2004 |

---

**Background:** The NDA for Ambien (NDA 19-908) was approved on December 16, 1992 by the Division of Neuropharmacological Drug Products. The original Pharmacology Toxicology review was conducted by Dr. Ann Wilk. Her review of the Segment II (embryo-fetal development) study in the rabbit noted an increase in postimplantation loss in the high dose dams (21.1% loss compared to 10.1% loss in control animals). The review also noted the following clinical signs in the treated dams "slight sedation in MD within 5 minutes lasting less than 2 hours. More marked sedation in HD of similar duration." Likewise, there was a dose-related decrease in mean weight gain in the dams over the course of the treatment period (HD dams gained a mean of 86 grams from Day 0 to Day 28 compared to a mean gain of 212 grams in the control animals over the same time period).

The sponsor appears to have proposed a Pregnancy Category – at the time of NDA submission; however, Dr. Wilk's initial review recommended a Pregnancy Category – This change was accompanied by a reference to the

the label that [redacted]

[redacted] As such, these recommendations appear to be based, at least in some part, on class labeling.

In the letter to the sponsor from Robert Temple, M.D., the Director of the Office of Drug Evaluation 1, dated April 21, 1992, the attached draft label included a Pregnancy Category [redacted] Lorex Pharmaceuticals, however, responded that they "do not agree with the modifications proposed" during labeling negotiations and further stated that they "continue to believe that there is not a sufficient basis to [redacted] and therefore did not accept either the recommendations for the [redacted]. Although it is not clear to me from the Division File, agreement with a Pregnancy Category B appears to have been made, since the approval letter dated December 16, 1992 from Robert Temple, M.D., contains the B categorization.

During the review of the proposed label for NDA 21-774, Adam Wasserman, Ph.D. noted several discrepancies in the exposure ratios for the carcinogenicity sections as well as the reproductive toxicology sections of the labeling. Once corrected, Dr. Wasserman and I forwarded the revised sections to Dr. Lois Freed, the supervisory pharmacologist in the Division of Neuropharmacology, who will be taking over responsibility for this drug product in August of 2005. Upon review of our proposed labeling changes, Dr. Freed (and Dr. Ed Fisher of the same Division) indicated that they agree with the revised dose ratios, and that, based upon the data contained in the original review, believe a Pregnancy Category of C should be assigned to this drug. Dr. Wasserman and I both concur. The Pregnancy Category C is consistent with the description of this category that is published in the US Code of Federal Regulations.

Title 21 CRF § 201.57 reads as follows:

> If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefit from use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

I believe that an increase in post-implantation losses alone, regardless of the mechanism of the effect (i.e. directly on the embryo or indirectly through maternal toxicity), should be considered an embryocidal effect. As such, it is my recommendation that the label for Ambien CR [redacted] be changed to reflect the labeling proposed by Dr. Wasserman.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

R. Daniel Mellon
4/1/05 04:26:44 PM
PHARMACOLOGIST

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: | **21-774** |
| SERIAL NUMBER: | **000** |
| DATE RECEIVED BY CENTER: | **06/08/04** |
| PRODUCT: | **Ambien CR (Zolpidem MR) 12.5/6.5 mg** |
| INTENDED CLINICAL POPULATION: | **— .reatment of insomnia characterized by difficulties with sleep initiation and/or maintenance** |
| SPONSOR: | **Sanofi-Synthelabo, Inc.** |
| DOCUMENTS REVIEWED: | **Vol 1. of 1** |
| REVIEW DIVISION: | **Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)** |
| PHARM/TOX REVIEWER: | **Adam M. Wasserman, Ph.D.** |
| PHARM/TOX SUPERVISOR: | **R. Daniel Mellon, Ph.D.** |
| DIVISION DIRECTOR: | **Bob Rappaport, M.D.** |
| PROJECT MANAGER: | **Sara Stradley** |

Date of review submission to Division File System (DFS): 3/31/2005

# *TABLE OF CONTENTS*

# *EXECUTIVE SUMMARY*

## A. RECOMMENDATION ON APPROVABILITY

From a Pharmacology/Toxicology perspective this New Drug Application may be approved.

## B. RECOMMENDATION FOR NONCLINICAL STUDIES

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

## C. RECOMMENDATIONS ON LABELING

**Note: The recommended labeling changes outlined below represent the pharmacology/toxicology review team's thoughts on these issues at the time of this review submission. As such, labeling negotiations have not yet occurred, and therefore the wording in the final approved label may differ from that below.**

**Pharmacodynamics:** Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) receptor.

zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, In contrast to the benzodiazepines, which nonselectively bind to and activate all receptor subtypes, zolpidem in vitro binds the receptor preferentially with a high affinity ratio of the $alpha_1/alpha_5$ subunits. The receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the 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 at hypnotic doses.

**Carcinogenesis, mutagenesis, impairment of fertility**

***Carcinogenesis***: Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley ratsfor 2 years at dietary dosages of 4, 18, and 80 mg base/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day , respectively, and 40 and 80 times the MRHD of Ambien CR 12.5 mg [10 mg zolpidem base], respectively, on a $mg/m^2$ basis).

***Mutagenesis***: Zolpidem did not have mutagenic activity in several tests including an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* mammalian gene forward mutation assay in mouse lymphoma cells, and an *in vitro* unscheduled DNA synthesis assay in rat hepatocytes. Zolpidem was not clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes or in an *in vivo* micronucleus test in mice.

***Impairment of fertility***: Zolpidem tartrate was administered by oral gavage to Sprague-Dawley rats at doses of 4, 20 or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on post partum Day 25. Zolpidem administered at 100 mg base/kg was associated with irregular estrus cycles and prolonged precoital intervals but did not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day , 20 times the MRHD of Ambien CR, , on a $mg/m^2$ basis).

***Drug/Laboratory test interactions:*** Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

## Carcinogenesis, Mutagenesis, and Impairment of Fertility

***Carcinogenesis:*** Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley rats for two years at dietary dosages of 4, 18, and 80 mg/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day (40 and 80 times the maximum recommended human dose [MHRD] of Ambien CR 12.5 mg [10 mg zolpidem base], respectively, on a $mg/m^2$ basis).

***Mutagenesis:*** Zolpidem did not have mutagenic activity in several tests including an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* mammalian gene forward mutation assay in mouse lymphoma cells, and an *in vitro* unscheduled DNA synthesis in rat hepatocytes. Zolpidem was not clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes or in an *in vivo* micronucleus test in mice.

***Impairment of Fertility:*** Zolpidem tartrate was administered by oral gavage to Sprague-Dawley rats at doses of 4, 20, or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on post partum Day 25. Zolpidem administered at 100 mg base/kg was associated with irregular estrus cycles and prolonged pre-coital intervals, but did not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day (20 times the MRHD of Ambien CR on a $mg/m^2$ basis).

## Pregnancy

***Teratogenic effects:*** Pregnancy Category C.

Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg based/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal and embryo/fetal toxicity was 4 mg base/kg/day (4 times the MRHD of Ambien CR on a $mg/m^2$ basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (up to 30 times the MRHD of Ambien CR, on a $mg/m^2$ basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternebrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal

**Pregnancy**

***Teratogenic effects***: Pregnancy Category C.
Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20 or 100 mg base/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal and embryo/fetal toxicity was 4 mg base/kg/day — 4 times the MRHD of / — Ambien CR, — on a mg/m$^2$ basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4 or 16 mg base/kg/day by oral gavage (up to — . 30 times the MRHD of — , Ambien CR, — n a mg/m$^2$ basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was below 1 mg base/kg/day (< 2-times the MRHD of — Ambien CR, — , on a mg/m$^2$ basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day — 8 times the MRHD of — Ambien CR — , on a mg/m$^2$ basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg and higher. Decreased maternal body weight gain as well as evidence of non-secreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg and higher and decreased pup survival at maternal doses of 100 mg base/kg. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg : 4 times the MRHD of / . Ambien CR, /, on a mg/m$^2$ basis).

There are no adequate and well-controlled studies in pregnant women. Zolpidem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
***Nonteratogenic effects***: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of 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 of mothers who received sedative/hypnotic drugs during pregnancy.

## II. Summary of nonclinical findings

### A. Brief overview of nonclinical findings

Nonclinical studies were not conducted, nor required, in support of this NDA.

### B. Pharmacologic activity

There were no new studies conducted for the purpose of characterizing zolpidem pharmacology. Zolpidem has been characterized as an agonist at the benzodiazepine binding site on $GABA_A$ receptors with preferential affinity for the GABA-BZ receptor expressing the $\omega_1$-subtype $\alpha$-subunit. The $GABA_A$ receptor represents the most significant inhibitory input in the central nervous system and is found within neural structures underlying sleep physiology and throughout the

brain. The demonstration of *in vitro* selectivity of zolpidem for a subset of $GABA_A$ receptors has been demonstrated in animal studies to have less anticonvulsant and myorelaxant properties and is thought to provide in humans a reduction in side effects commonly observed with benzodiazepines as used in the treatment of insomnia.

C. NONCLINICAL SAFETY ISSUES RELEVANT TO CLINICAL USE

There are no novel nonclinical safety issues presented by the clinical use of the controlled release form of zolpidem.



APPEARS THIS WAY
ON ORIGINAL

# *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

## 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 21-774
**Review number**: 1
**Sequence number/date/type of submission**: 000/June 8, 2004/Original
**Information to sponsor**: Yes ( ) No (X)
**Sponsor and/or agent**: Sanofi-Sythelabo, Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

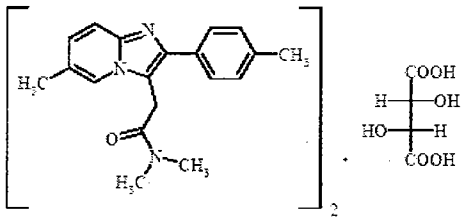
**Manufacturer for drug substance**:

**Reviewer name**: Adam M. Wasserman, Ph.D.
**Division name**: Anesthetic, Critical Care, and Addiction Drug Products
**HFD #**: 170
**Review completion date**: March 25, 2005

**Drug**:

Trade name: Ambien CR
Generic name: Zolpidem tartrate
Code name: SL80.0750-23N
Chemical name: N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1)
CAS registry number: 99294-93-6
Molecular formula/molecular weight: $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ / 764.88

Structure:



**Relevant INDs/NDAs/DMFs**:
NDA: 19-908
IND: 25,361
DMF: —

**Drug class**: Sedative/Hypnotic

**Indication**: — treatment of insomnia

**Clinical formulation**: Ambien CR contains either 6.25 mg or 12.5 mg of zolpidem tartrate in a controlled release tablet for oral administration. Ambien CR consists of a coated two layer tablet: one layer releases its drug content immediately and another layer that allows a slower release of zolpidem tartrate. The 6.25-mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate and titanium dioxide. The 12.5-mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide and yellow ferric oxide. The percent composition is shown in the Sponsor's table below.

Table (3.2.P.1.5) 2 - Pooled unit and percent compositions of 6.25 mg Zolpidem-MR tablets

| Components | Unit (mg) | Percent (%) [a] |
|---|---|---|
| Zolpidem tartrate | 6.250 | |
| Lactose monohydrate | | |
| Microcrystalline cellulose | | |
| Hypromellose | | |
| Potassium bitartrate | | |
| Sodium starch glycolate | | |
| Magnesium stearate | | |
| Titanium dioxide | | |
| Polyethylene glycol | | |
| Colloidal silicon dioxide | | |
| Ferric oxide, red | | |
| **Total** | **260.000** | **100.00** |

[a] Calculated from the unit composition of the whole tablet.

Table (3.2.P.1.6) 2 - Pooled unit and percent compositions of 12.5 mg Zolpidem-MR tablets

| Components | Unit (mg) | Percent (%) [a] |
|---|---|---|
| Zolpidem tartrate | 12.500 | |
| Lactose monohydrate | | |
| Microcrystalline cellulose | | |
| Hypromellose | | |
| Potassium bitartrate | | |
| Sodium starch glycolate | | |
| Magnesium stearate | | |
| Titanium dioxide | | |
| Polyethylene glycol | | |
| Indigo carmine – aluminum lake | | |
| Colloidal silicon dioxide | | |
| Ferric oxide, yellow | | |
| **Total** | **260.000** | **100.00** |

[a] Calculated from the unit composition of the whole tablet.

The controlled release formulation of Ambien CR contains several excipients not found in Ambien including potassium bitartrate — colloidal silicon dioxide — and FD&C Blue #2 ( — · in the coating. These excipients are contained in

higher amounts in FDA-approved products with an oral route of administration or are listed as GRAS in 21CFR Part 582 "***Substances Generally Recognized As Safe***".

**Route of administration**: Oral tablet

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

**Studies reviewed within this submission:**
No nonclinical studies were submitted in support of this NDA.



APPEARS THIS WAY
ON ORIGINAL

## 2.6.2 PHARMACOLOGY

**2.6.2.1 Brief summary**
No new nonclinical studies were submitted in support of NDA 21-774. Please see the original Ambien review, NDA 19-908 for information on zolpidem tartrate.

**2.6.2.2 Primary pharmacodynamics**
**2.6.2.3 Secondary pharmacodynamics**
**2.6.2.4 Safety pharmacology**
**2.6.2.5 Pharmacodynamic drug interactions**
No new nonclinical information as described above.

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

**2.6.4.1 Brief summary**
No new nonclinical studies were submitted in support of NDA 21-774. Please see the original Ambien review, NDA 19-908 for information on zolpidem tartrate.

**2.6.4.2 Methods of Analysis**
**2.6.4.3 Absorption**
**2.6.4.4 Distribution**
**2.6.4.5 Metabolism**
**2.6.4.6 Excretion**
**2.6.4.7 Pharmacokinetic drug interactions**
**2.6.4.8.1 Other Pharmacokinetic Studies**
**2.6.4.9 Discussion and Conclusions**
**2.6.4.10 Tables and figures to include comparative TK summary**
No new nonclinical information provided as described above.

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

## 2.6.6 TOXICOLOGY

**2.6.6.1 Overall toxicology summary**
No new nonclinical studies were submitted in support of NDA 21-774. Please see the original Ambien review, NDA 19-908 for information on zolpidem tartrate.

**2.6.6.2 Single-dose toxicity**
**2.6.6.3 Repeat-dose toxicity**
**6.6.6.4 Genetic toxicology**
**2.6.6.5 Carcinogenicity**
**2.6.6.6 Reproductive and developmental toxicology**
**2.6.6.7 Local tolerance**
**2.6.6.8 Special toxicology studies**
**2.6.6.9 Discussion and Conclusions**
**2.6.6.10 Tables and Figures**
No new nonclinical information provided as described above.

## 2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

**CONCLUSIONS**: This NDA application may be approved from a Pharm/Tox perspective as no new nonclinical studies were conducted.

**UNRESOLVED TOXICOLOGY ISSUES**: None.

**RECOMMENDATIONS**: The proposed label should be revised and a separate label for Ambien CR should be considered.

**SUGGESTED LABELING**: See Executive Summary.

**SIGNATURES**:
Reviewer Signature: Adam M. Wasserman, Ph.D.

Supervisor Signature: _____ Concurrence: Yes ___ No ___

## APPENDIX/ATTACHMENTS

N/A

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

Adam Wasserman
4/1/05 01:19:40 PM
PHARMACOLOGIST

R. Daniel Mellon
4/1/05 03:11:28 PM
PHARMACOLOGIST
I concur.