NDA 19, 908 (022)
AMBIEN PEDIATRIC SUPPLEMENT

Clinical Pharmacology Review

NDA:	19-908, (b) (4) (022)
Brand Name:	Ambien
Generic Name:	Zolpidem tartrate
Type of Dosage Form:	Tablets
Strengths:	5 mg, 10 mg
Indications:	Insomnia
Type of Submission:	(b) (4)
Sponsor:	Sanofi Aventis
Submission Date:	9/29/06
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCP Team Leader:	Ramana Uppoor, PhD

Table of Contents

1 Executive Summary

1.1 Recommendations

We have reviewed the pharmacokinetic data from clinical pharmacology study L8749 that evaluated the pharmacokinetics/pharmacodynamics of zolpidem in 64 children aged 2-18 y.o. The study was conducted prior to issuance of the Written Request that is subject of this NDA, and although the study was not requested as part of the Written Request, the results have been included in this submission.

The results of study EFC6820 entitled "Efficacy, Safety and Tolerability of Zolpidem in the Treatment of Children aged 6-17 Years with ADHD-Associated Insomnia", conducted to address the Written Request", did not show a significant effect of zolpidem on latency to persistent sleep compared to placebo, as measured by polysomnography. This study was not reviewed by OCP.

Recommendation

(b) (4)

OCP recommends changes to the "Highlights" section of the labeling. Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 4** of this review for OCP recommendations)

1.2 *Phase 4 Commitments*

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

NDA 19-908 (b) (4) (022) was submitted to provide final study reports in fulfillment of the Pediatric Written Request of July 31, 2006. Prior to issuance of the Written Request, the Sponsor conducted study L8749 entitled "Single Dose Pharmacokinetic and Pharmacodynamic Evaluation of Three Different Doses in Children from 2 to 18 years of Age" that evaluated the PK of an orally administered aqueous formulation of zolpidem in the pediatric population. This study was not considered part of the written request, but has been reviewed by the Office of Clinical Pharmacology as part of the submission.

The key findings with respect to the conduct of the PK study and the Clinical Pharmacology of zolpidem in the pediatric population:

- Subjects were reasonably distributed across age groups and by gender.
- Cmax and AUC were the only dose-dependent PK parameters.
- AUC, half-life, and clearance were age related.
- The mean Cmax from the 0.25 mg/kg dose was 192.7 ng/ml, 150.3 ng/ml and 185.2 ng/ml for each age group (2-6 y.o., > 6-12 y.o., and > 12-18 y.o, respectively) and this is

in the range of Cmax in healthy adults (mean 121 ng/ml and range 58-272 ng/ml) following a 10 mg dose according to the Ambien labeling.

- Mean tmax for the 0.25 mg/kg dose was 1.0, 1.0, and 1.4 hours for each of the age ranges in pediatrics in comparison to the mean tmax of 1.6 hours in healthy adults described in the Ambien labeling.
- Mean half-life was 1.4, 2.0, and 2.3 hours for each pediatric age groups (2-6 y.o., > 6-12 y.o., and > 12-18 y.o, respectively) in comparison to 2.5 hours in adults described in the Ambien labeling.

Pediatric Written Request

The results of study EFC6820 entitled "Efficacy, Safety and tolerability of zolpidem in the treatment of Children aged 6-17 Years with ADHD-Associated Insomnia", conducted to address the Written Request" did not show a significant effect of zolpidem on latency to persistent sleep compared to placebo, as measured by polysomnography. The proposed label states that safety and effectiveness for zolpidem has not been established in pediatric patients. (b) (4)

Recommendations

(b) (4)

OCP recommends several changes to the "Highlights" section of the labeling.

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Reviewer, Neurology Drug Products, DCP I
Office of Clinical Pharmacology

Concurrence: Ramana Uppoor, PhD
Team Leader, Neurology Drug Products, DCP I
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cc: HFD-120 NDA 19-908 (022)
CSO/C. Michaloski
/Biopharm/S. Yasuda
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HFD-860 /DD DCP1/M. Mehta

2 Question-Based Review

What are the general attributes?

Zolpidem tartrate is a non-benzodiazepine hypnotic that is indicated for short-term treatment of insomnia in adults.

What is the pediatric target population for zolpidem?

The target population was pediatric patients (aged ≥6-≤17 y.o.) with insomnia associated with attention-deficit hyperactivity disorder (ADHD).

What are the pharmacokinetic characteristics of zolpidem in children?

The PK results are shown in the tables below, as provided by the Sponsor.

Table (10.4.1.2) 1b: Mean (SD) Cmax (ng/mL)

	2 to 6	>6 to 12	>12 to 18	Overall by dose
0.125	102.5 (42.5)	103.5 (77.8)	132.9 (43.4)	112.0 (56.3)
0.25	192.7 (108.9)	150.3 (53.7)	185.2 (72.2)	177.3 (80.4)
0.50	243.8 (93.3)	240.9 (126.3)	252.7 (94.7)	245.8 (100.5)
Overall by age	179.7 (101.4)	165.6 (106.1)	193.1 (86.3)	179.5 (97.4)

Table (10.4.1.2) 1c: Mean (SD) Tmax (hr)

	2 to 6	>6 to 12	>12 to 18	Overall by dose
0.125	1.0 (0.4)	0.9 (0.6)	1.6 (0.3)	1.1 (0.9)
0.25	1.0 (0.4)	1.0 (0.6)	1.4 (0.5)	1.1 (0.5)
0.50	0.6 (0.2)	1.4 (0.6)	1.1 (0.4)	1.0 (0.5)
Overall by age	0.9 (0.4)	1.1 (0.6)	1.3 (0.8)	1.1 (0.6)

Table (10.4.1.2) 1d: Mean (SD) AUC 0 to $_{\infty}$ (ng/mL*hr)

	2 to 6	>6 to 12	>12 to 18	Overall by dose
0.125	359.7 (210.3)	420.0 (368.2)	572.9 (180.0)	444.8 (270.9)
0.25	649.3 (582.3)	723.6 (379.2)	977.0 (315.9)	786.3 (444.9)
0.50	655.5 (409.9)	1108.3 (445.7)	1179.1 (502.8)	981.0 (792.3)
Overall by age	554.8 (430.6)	752.0 (480.6)	926.5 (428.7)	741.3 (465.6)

Table (10.4.1.2) 1e: Mean (SD) Half Life (hr^{-1})

	2 to 6	>6 to 12	>12 to 18	Overall by dose
0.125	2.2 (1.2)	2.1 (0.6)	2.3 (0.8)	2.2 (0.9)
0.25	1.4 (0.7)	2.0 (0.8)	2.3 (0.4)	1.9 (0.7)
0.50	1.7 (0.7)	2.8 (0.8)	2.3 (0.6)	2.3 (0.8)
Overall by age	1.8 (0.9)	2.3 (0.8)	2.3 (0.6)	2.1 (0.8)

Table (10.4.1.2) 1g: Mean (SD) Clearance (mL/min/kg)

	2 to 6	>6 to 12	>12 to 18	Overall by dose
0.125	7.4 (3.8)	12.4 (16.8)	3.9 (1.1)	8.1 (10.3)
0.25	11.1 (7.3)	7.0 (3.0)	4.7 (1.6)	7.6 (5.3)
0.50	16.8 (9.4)	9.3 (5.3)	5.6 (2.6)	10.6 (7.7)
Overall by age	11.7 (7.9)	9.7 (10.3)	4.8 (2.0)	8.8 (8.0)

24 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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2/28/2007 11:46:18 AM
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