

BPCA Clinical Pharmacology Summary

NDA:	19-908, SE5 (022)
Brand Name:	Ambien
Generic Name:	Zolpidem tartrate
Type of Dosage Form:	Tablets
Strengths:	5 mg, 10 mg
Indications:	Insomnia
Type of Submission:	Pediatric Exclusivity sNDA
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

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

OCP recommends that the results of the PK study in children should not be described in the label since safety and effectiveness have not been established in pediatric patients (the Sponsor has not proposed changes to the clinical pharmacology sections of the label).

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

NDA 19-908 SE5 (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 are:

- Subjects were reasonably distributed across age groups and by gender.
- C_{max} and AUC were the only dose-dependent PK parameters.
- AUC, half-life, and clearance were age related.
- The mean C_{max} 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 C_{max} in healthy adults (mean 121 ng/ml and range 58-272 ng/ml) following a 10 mg dose according to the Ambien labeling.
- Mean t_{max} 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 t_{max} 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.

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

/s/

Ramana S. Uppoor
3/19/2007 11:09:22 AM