# CLINICAL REVIEW

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| Application Type | Efficacy Supplement |
| Submission Number | 022 |
| Submission Code | SE5 |
| Letter Date | September 29 2006 |
| Stamp Date | September 29 2006 |
| PDUFA Goal Date | March 29 2007 |
| Reviewer Name | D. Elizabeth McNeil, MD |
| Review Completion Date | February 2 2007 |
| Established Name | zolpidem tartrate tablets |
| (Proposed) Trade Name | Ambien |
| Therapeutic Class | Hypnotic |
| Applicant | sanofi-synthelabo |
| Priority Designation | P |
| Formulation | Liquid formulation |
| Dosing Regimen | 0.25 mg/kg (max 10 mg/day) |
| Indication | Insomnia |
| Intended Population | Pediatric patients with ADHD associated-insomnia |

# Executive Summary

## 1.1 Recommendation on Regulatory Action

The sponsor proposed that efficacy and safety information from the pediatric clinical trial should be included in the Ambien label. The agency has approved that language for inclusion in the approved labeling. The submitted efficacy study did not demonstrate efficacy in the pediatric population so no pediatric indication should be granted; Ambien is not approved for use in the pediatric population.

There are safety concerns about the use of Ambien in the pediatric population, especially in patients under 12 years old. The incidence of hallucinations in pediatric patients treated with zolpidem was unacceptably high (7.4%) in comparison with the incidence in patients treated with placebo (0%); for comparison, in adults the incidence of hallucinations was less than 1% in pre-marketing trials.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

There is no recommended risk management activity for this product.

### 1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this product.

### 1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests for this product

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Zolpidem tartrate is an imidazopyridine class hypnotic currently marketed as an immediate release formulation under the trade name Ambien (NDA 19-908) by Sanofi-synthelabo.

The sponsor submitted one Phase III study, EFC 6820, a double-blind, randomized, placebo-controlled, parallel group study comparing the efficacy and safety of zolpidem to placebo in pediatric patients with ADHD-associated insomnia.

### 1.3.2 Efficacy

This study did not demonstrate efficacy in the pediatric population as it failed on its primary endpoint, decreased latency to persistent sleep.

### 1.3.3 Safety

There were no deaths reported during this clinical development program.

The treatment emergent adverse events (TEAE) which both occurred at an incidence of >5% and occurred at a greater incidence in treated rather than placebo patients were headache, dizziness and hallucinations. The first two TEAE were consistent with what is reported in the Ambien label. The latter adverse event was not a significant occurrence during the adult pre-marketing studies and so does not have a prominent place in the label. Hallucinations have been reported as a frequent post-marketing occurrence in adults, though they were reported by 1% or fewer of the adult participants during the pre-marketing trials.

Hallucinations were the most common adverse event leading to patient discontinuation from this pediatric study. All of the patients who reported hallucinations were in the zolpidem treatment arm. The events started within 60 minutes of dose ingestion and were not limited to initial drug exposure, occurring as early as Day 1 to as late as Day 30 of the double-blind period.

No significant next-day residual effects on objective measures or on subjective measures were seen.

### 1.3.4 Dosing Regimen and Administration

The study did not establish a safe and effective dose of Ambien for use in the pediatric population.

### 1.3.5 Drug-Drug Interactions

The current Ambien label addresses interactions seen with CNS-active drugs as well as cimetidine, ranitidine, and digoxin.

### 1.3.6 Special Populations

Age
All of the study participants were under the age of 18 years. While there was no overall difference in the rate of adverse events, the incidence of hallucinatory experiences was higher in the younger age group when the incidence in patients under 12 years old were compared to that seen in patients who were over 12 years old.

Ethnicity

The number of non-Caucasian participants was too small to make any comments on possible interactions of drug and ethnicity.

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