CLINICAL REVIEW

Application Type	(b) (4)
Submission Number	022
Submission Code	(b) (4)
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

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

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The submitted efficacy study did not demonstrate efficacy 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. It is not inconceivable that hallucinatory experiences at bedtime might cause a fear-based reluctance to go to sleep and further exacerbate the baseline insomnia in susceptible pediatric patients.

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.

There was a single serious adverse event (SAE) reported during the Phase I study; a boy fell 40 hours after ingestion of 0.25 mg/kg of zolpidem and sustained an ecchymosis on his left hand.

There was also one SAE reported during the Phase 3 study; an 11 year old boy (placebo group) was hospitalized due to "impulse-control disorder" on day 6 of the double-blind treatment period. He was noted to have concomitant major depressive disorder and oppositional defiant disorder at the time of his hospitalization. At baseline, he had ADHD and insomnia.

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.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolpidem tartrate is an imidazopyridine class hypnotic with an affinity for the benzodiazepine (BZ_1) receptor of $GABA_A$. It is currently marketed, by Sanofi-synthelabo, as an immediate release formulation under the trade name Ambien (NDA 19-908) as well as a modified release preparation of zolpidem tartrate, Ambien CR. Ambien is currently indicated for the treatment of insomnia characterized by difficulties with sleep initiation. Ambien CR is indicated for the treatment of insomnia characterized by difficulties with sleep initiation and/or sleep maintenance.

2.2 Currently Available Treatment for Indication

Currently there are multiple FDA approved products indicated for the treatment of chronic insomnia including Halcion (triazolam), Prosom (estazolam), Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone), Ambien CR (zolpidem tartrate) and Rozerem (ramelteon).

A number of other products are used off-label to treat chronic insomnia e.g. tricyclic antidepressants, anxiolytics, and antihistamines.

There are currently no sedative-hypnotics which have been studied in and approved for use in the pediatric population.

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is currently being marketed by Sanofi-synthelabo as Ambien and as Ambien CR.

2.4 Important Issues With Pharmacologically Related Products

There have been labeling changes in association with the approved hypnotics due to safety or effectiveness concerns. In February 2006, the Division of Neurology Products issued letters to the manufacturers of approved sedative-hypnotics indicating class labeling changes, standardizing the indications and usage sections as well as modifying the WARNINGS section and the DRUG ABUSE AND DEPENDENCE section. Additionally, in December 2006 the sedative-hypnotic group was given new class labeling language to address the issues of "sleep-driving and possible anaphylactic reactions." Medication guides for this drug group will be required in the future.

The safety concerns associated with the hypnotics include next-day residual effects as well as neuropsychiatric adverse events such as confusion, amnesia, hallucinations, and worsening of psychiatric disorders, especially when the medications are not taken immediately before bedtime.

The next-day residual effects on attention and vigilance are evaluated during the development plan for drugs in the sedative/hypnotic group. Some sponsors are beginning to develop methods to specifically evaluate next-day driving ability.

The known neuropsychiatric adverse events are predominantly handled through labeling. These labels for these drugs all specify that the drug is to be taken at bedtime. When people do not take the drug immediately before bed, they may experience confusion as well as lacunar amnesia for their actions between ingestion of the pill and actually falling asleep.

Ambien has been reported (http://www.erowid.org/pharms/zolpidem/zolpidem.shtml) to provide the following sensations when used at a time other than right before going to sleep: a transient sense of "social togetherness", loss of inhibition, thinking difficulties, balance difficulties, loss of motor control, amnesia, heightened sense of relaxation, dissociation, distorted depth perception and visual/auditory hallucinations. [*Reviewer's note: These reports are spontaneous accounts of off-label use.]*

2.5 Presubmission Regulatory Activity

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2.6 Other Relevant Background Information

There is no other relevant background information for this application.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No CMC review was performed in support of this application.

3.2 Animal Pharmacology/Toxicology

Dr. Melissa Banks is the pharmacology/toxicology reviewer who reviewed the included preclinical data. The interested reader is referred to her review for a discussion of the preclinical findings in the juvenile animal studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source for clinical data was the material submitted by the sponsor in support of this application.

4.2 Tables of Clinical Studies

Table 1: Clinical studies

	Study population	PK/PD data	Efficacy data	Safety data
L8749	Pediatric patients	X		X
EFC 6820	Pediatric patients		X	X

4.3 Review Strategy

The sponsor's submission was emphasized in this review, with particular emphasis paid to the efficacy trial: EFC6820. Both pediatric trials were included in the analysis of safety.

I, Dr. D. Elizabeth McNeil, was responsible for the synthesis and documentation of the overall conclusions of this application.

Dr. Sally Yasuda, of the Office of Clinical Pharmacology and Biopharmaceutics, reviewed the pharmacokinetics data.

Dr. Melissa Banks was the pharmacology/toxicology reviewer who reviewed the preclinical data.

4.4 Data Quality and Integrity

We did not select sites for inspection in relation to this study. If we were to have done so, we would have inspected the site headed by Dr. Vance (18 patients enrolled; 5-placebo, 13-active drug) and the site headed by Dr. Boellner (27 patients enrolled; 10-placebo, 17-active drug). The patients enrolled by these sites represented 23% of the placebo patients and 22% of the active drug group.

While it was noted that almost a quarter of the entire study population was accrued by two of the PIs (Drs. Vance and Boellner), the study failed and so the results from these sites were unlikely to have favorably influenced the result.

4.5 Compliance with Good Clinical Practices

The sites appear to have been in compliance with good clinical practices (GCP).

4.6 Financial Disclosures

We obtained financial disclosure information from the principal and sub- investigators for study EFC 6820.

Sanofi-Synthelabo submitted certification of the absence of disclosable interests (form 3454) for all of the Principal Investigators and their sub-investigators.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A pharmacokinetics review is being performed by Dr. Sally Yasuda. The interested reader is referred to her final review for a detailed review of the pharmacokinetics of this product in the pediatric population.

5.2 Pharmacodynamics

A pharmacodynamics review is being performed by Dr. Sally Yasuda. The interested reader is referred to her final review for comments on the pharmacodynamics of this product in the pediatric population.

Zolpidem, though not a benzodiazepine, shares some of the pharmacological properties of the benzodiazepines. It interacts with the GABA-BZ receptor complex, preferentially binding the sigma 1(ω1) receptor. This receptor is present in the substantia nigra (pars reticulata), ventral thalamic complex, pons, and globus pallidus, among other places.

5.3 Exposure-Response Relationships

Prior to initiating the efficacy trial, the sponsor completed a single dose open-label pharmacokinetic and pharmacodynamic evaluation of three different zolpidem doses in children from 2 to 18 years old: L8749. To be eligible for study participation children had to meet all of the following key criteria: a complaint of significant difficulty (defined by frequency, severity and/or chronicity) initiating or maintaining sleep; sleep disturbance must have been causing clinically significant impairment in school performance, behavior, learning or development or the child as reported by the child and/or caregiver; sleep disturbance did not occur in the context of an intrinsic dyssomnia, a circadian rhythm disorder or a parasomnia; sleep disturbance was not attributable to either the direct physiologic effect of a drug of abuse or misuse of a prescribed medication.

Zolpidem was dosed at 0.125, 0.25 and 0.5 mg/kg up to a maximum dose of 20 mg. Children had a baseline PSG as well as a PSG on the night of study drug administration. A sleep diary was kept from screening through the day of drug administration. Overnight actigraphy was to be done nightly from the screening visit through the day of study drug administration. This study measured C_{max}, T_{max}, drug half-life, and AUC as well as estimating the apparent volume of distribution and the apparent clearance. The pharmacodynamic measures included the following sleep parameters: time to sleep(TS), duration of sleep period, sleep efficiency, frequency of shifts between seep stages, number and duration of awakenings. Sleep stages and non-REM/REM cycle parameters were measured. Sleep onset latency, REM latency and SWS latency were also evaluated.

Results from trial L8749

	0.125 mg/kg	0.25 mg/kg	0.5 mg/kg
Age groups			
2-6 years	7	7	7
>6-12 years	7	7	7
>12 to 18 years[a]	7	7	8
ADD/ADHD[b]	5	4	5
NDD[c]	5	0	0

a All of the children in this group received the maximum dose of 20 mg
b 8 of these children were in the middle age group with 4 in the youngest group and 2 in the oldest group
c 3 of these children were in the middle group and 2 were in the youngest group

Adverse events from trial L8749:

	0.125 mg/kg n=21	0.25 mg/kg n=21	0.5 mg/kg n=22
Treatment-Emergent AE (possibly related)			
Tachycardia	0	0	1
Abnormal eye movements	0	0	2
Diplopia	0	0	1
Anxiety	1	1	0
Disorientation	0	0	1
Hallucinations	0	0	2
Dizziness	0	3	0
Diarrhea/loose stool	2	0	1
Elevated Bilirubin	1	0	0
Obstructive breathing	0	0	1
Hiccups	0	0	1

No deaths occurred.

The only serious adverse event reported was an 8 year old boy (subject 8-015, dose 0.25 mg/kg) who fell 40 hours after receiving zolpidem and bruised his left hand.

Two children withdrew from the study due to an adverse event. A four year old boy received his dose then required almost 4 hours to fall asleep. He rested quietly for 2 hours before awakening in an agitated state. He was discharged from the study prior to completion of the scheduled blood draws. He had had 5 mg of zolpidem in the past and had manifested a similar response according to his mother. The investigator felt that this was an expected effect "due to the dose of zolpidem being too low." A 9 year old girl in the 0.25 mg/kg group complained of dizziness 15 minutes after dosing then became anxious. She was released, wide awake, 2 hours after dosing. She fell asleep approximately 4.75 hours after dosing.

Sleep parameters from trial L8749:

Sleep parameter	Visit	N	Mean	SD	Mean change from baseline	SD
Sleep latency (min)	Baseline	65	36.7	59.18		
	Drug	64	41.0	46.41	4.9	45.46
True sleep time (min)	Baseline	65	410.6	98.67		
	Drug	64	432.9	122.85	24.5	98.29
Sleep efficiency (%)	Baseline	65	83.4	16.2		
	Drug	64	81.7	17.88	-1.7	12.3
Total sleep time (min)	Baseline	65	456.9	86.1		
	Drug	64	487	98.57	32.2	91.90

Sponsor's conclusions:

- Pediatric patients both absorb and clear zolpidem more rapidly than adult patients. A dose of 0.25 mg/kg "was associated with a PK profile within the range of that observed in adults following 10 mg and up to 20 mg (p.32 of the study report for EFC 6820)"
- Overall, sleep latency had a mean increase of 4.9 minutes. True sleep time and total sleep time both had a mean increase of approximately 30 minutes. Sleep efficiency decreased by 1-2 %. [*emphasis added*]
- While the 0.25 mg/kg dose increased true sleep time and total sleep time as compared to the 0.125 dose, increasing the dose to 0.5 mg/kg did not produce increased true sleep time or total sleep time. The 0.5 mg/kg dose appeared to result in an increased time to persistent sleep [*emphasis added*].
- The total and the true sleep times were both increased in the 14 ADD patients, but "the increase is not likely to be clinically significant." The total and the true sleep times were both decreased in the 5 NDD patients [*emphasis added*]. Due to the small numbers and lack of a placebo comparison group, the sponsor decided that these results need further investigation.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor did not propose any changes to the approved indication for this product:

6.1.1 Methods

EFC 6820

The primary efficacy analysis for EFC6820 used the intent to treat (ITT) population which was defined as all patients who were randomized. The pre-specified primary efficacy variable was the change of LPS from baseline to the post-baseline PSG scheduled between Week 3 and Week 6

(coded as Week 4). The sponsor performed an ANCOVA analysis with two fixed effects (treatment group: zolpidem, placebo and age group: 6-11 years, 12-17 years) and baseline value as the covariate. The primary model did not factor in potential interactions between treatment and age group. A 2-sided significance level of 5% was used for the analysis.

6.1.2 General Discussion of Endpoints

The sponsor used the following definition for latency to persistent sleep (LPS)

- It was measured from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset).
- It was calculated as the number of epochs from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset) divided by 2

Reviewer's comments:
This is a standard definition for PSG recordings in studies of hypnotics and was acceptable for use in this study.

6.1.3 Study Design

Study EFC 6820 was a double-blind, randomized, placebo-controlled, parallel group study which compared the efficacy and safety of zolpidem to placebo in pediatric patients with ADHD-associated insomnia.

The primary efficacy variable was the mean change on polysomnogram (PSG) measured latency to persistent sleep.

6.1.4 Efficacy Findings

Study EFC6820
The sponsor's analysis demonstrated that the study failed on its primary endpoint: the mean change in LPS at week 4 after adjustments had been made for differences at baseline.

A sensitivity analysis was performed which also failed to distinguish between the treatment arms.

The approved analysis as specified in the statistical analysis plan called for a hierarchical procedure. The secondary endpoints were not considered significant due to the failure of the primary endpoint to demonstrate a significant result. The interested reader may find further discussion of these secondary results in the appendix to this review.

Table 1 :

Table (8.1.1) 1 - Change from baseline at Week 4 of latency to persistence sleep (LPS) (min: sec) - ITT population

	Placebo (N=65)	Zolpidem (N=136)
Baseline and post-baseline		
Number	60	124
Baseline		
Mean (SD)	76:37 (49:30)	70:48 (51:06)
Median	58:00	52:21
Min;Max	31:00; 263:00	30:06; 312:00
Change from baseline at week 4		
LS Mean (SE)	-21:16 (7:38)	-20:17 (5:17)
LS Mean Difference (SE)	-	0:58 (9:17)
95% CI	-	(-17:20 to 19:16)
p-value vs Placebo	-	0.9169

Note: Week 4 refers to evaluation planned between visit 5 and visit 7
Note : p-value comes from analysis of covariance using age and treatment as fixed effect and baseline value as covariate
PGM= SL80075023/EFC6820/CSR/BS/PGM RPT/C26 lpsChgBln.sas OUT= OUTPUT/C26 lpsChgBln 1.html (29AUG2006 - 9:52)

(taken from page 59 of study report)

Table 2 : LPS changes from baseline evaluated for potential age interaction

	Overall assessment (N=201)	Placebo (N=65)	Zolpidem (N=136)
P-value Treatment by Age interaction	0.9514	-	-
Change from baseline at week 4 per age group			
Number [6 to 11]		34	64
Number [12 to 17]		26	60
Aged 6 to 11 LS Mean (SE)	-	-22:15 (10:07)	-20:46 (7:27)
Aged 12 to 17 LS Mean (SE)	-	-20:10 (11:34)	-19:49 (7:39)
Aged 6 to 11 LS Mean Difference (SE)	-	-	1:29 (12:36)
Aged 6 to 11 95% CI	-	-	(-23:22 to 26:21)
Aged 6 to 11 p-value vs Placebo	-	-	0.9062
Aged 12 to 17 LS Mean Difference (SE)	-	-	0:21 (13:51)
Aged 12 to 17 95% CI	-	-	(-27:00 to 27:41)
Aged 12 to 17 p-value vs Placebo	-	-	0.9803
Change from baseline at week 4 for all age group			
Number		60	124
LS Mean (SE)	-	-21:13 (7:41)	-20:18 (5:18)
LS Mean Difference (SE)	-	-	0:55 (9:21)
95% CI	-	-	(-17:32 to 19:21)
p-value vs Placebo	-	-	0.9221

Note: Week 4 refers to evaluation planned between visit 5 and visit 7
Note : p-values come from analysis of covariance using age, treatment and age*treatment interaction as fixed effect and baseline value as covariate
PGM= SL80075023/EFC6820/CSR/BS/PGM RPT/C26 psgIntAge.sas OUT= OUTPUT/C26 psgIntAge 1.html (29AUG2006 - 9:53)

(taken from Appendix 14.2.6.1.1.2.1 of the study report, page 1097)

6.1.5 Clinical Microbiology

This section is not applicable to this efficacy supplement.

6.1.6 Efficacy Conclusions

Clinical reviewer's comments:
This study failed to demonstrate that use of zolpidem decreases the latency to persistent sleep in pediatric patients. Whilst there has been some thought that the dose was perhaps too low and therefore insufficient to produce the desired result, it does not seem to make sense that there was no apparent benefit in the older children either. The older patients might have been expected to have a response closer to that of adults.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths during the studies done in support of this application.

7.1.2 Other Serious Adverse Events (SAE)

[*Reviewer's note: The data used for this section consists of the sponsor's narrative summaries, line listings and case report forms. The relevant AE are highlighted with bold font.*]

Study L8749
The only serious adverse event reported was in an 8 year old boy (subject 8-015, dose 0.25 mg/kg) who fell 40 hours after receiving zolpidem and **bruised his left hand.**

Study EFC 6820
There was one SAE reported during the Phase 3 study; an 11 year old boy (placebo group) was hospitalized due to **"impulse-control disorder"** on day 6 of the double-blind treatment period. He was noted to have concomitant **major depressive** disorder and **oppositional defiant disorder** at the time of his hospitalization. At baseline, he had ADHD and insomnia.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Profile of dropouts from studies L8749 and EFC 6820[a]

Two patients withdrew from the pharmacokinetic study L8749; both discontinuations were due to adverse events.

Twenty-three patients withdrew from the clinical efficacy study, EFC 6820, as described below.

Table 3 : Reasons for discontinuation from the clinical efficacy study: EFC 6820

Reason	**Placebo (n=65)**	**Zolpidem (n=136)**
Total	**8 (12%)**	**15(11%)**
Lack of efficacy	0	4
Adverse event	0	9 (60%)
Poor compliance	0	1 (8%)
Subject request	8 (100%)	0
Other	0	1 (8%)

[a]The percentages in the rows other than the total row reflects the percentage of dropouts who discontinued for a given reason

Discontinuations in the placebo group:

- Subject 840022022 (exposed 13 days) discontinued at the subject's request due to a family emergency which prevented continuing in the study
- Subject 840006010 (exposed 45 days) discontinued at the subject's request due to an extended time out of town and inability to return to the study site
- Subject 840003013 (exposed 16 days) discontinued at the subject's request due to withdrawn consent when the mother got a new job
- Subject 840011005 (exposed 14 days) discontinued at the subject's request due to parent's refusal to return child to the study site
- Subject 840066008 (exposed 19 days) discontinued at the subject's request due to time constraints
- Subject 840069008 (exposed 7 days) discontinued at the subject's request due to "mom too busy"
- Subject 840002013 (exposed 62 days) discontinued at the subject's request: subject never returned to the study site
- Subject 840002029 (exposed 28 days) discontinued at the subject's request: subject never returned to the study site

Discontinuations in the zolpidem group:
Lack of efficacy:

- Subject 840001009 (exposed 7 days)

- Subject 840002028 (exposed 49 days)
- Subject 840030002 (exposed 7 days)
- Subject 840030009 (exposed 6 days)

Adverse event

- Subject 840009002 (exposed 1 day)
- Subject 840055004 (exposed 1 day)
- Subject 840045001 (exposed 2 days)
- Subject 840008011 (exposed 2 days) was discontinued due to poor compliance to protocol however, he complained of hallucinations while on study.
- Subject 840015001 (exposed 6 days)
- Subject 840002037 (exposed 6 days)
- Subject 840042007 (exposed 19 days)
- Subject 840051006 (exposed 25 days)
- Subject 840022012 (exposed 30 days)
- Subject 840017006 (exposed 45 days)

Other

- Subject 840001020 (exposed 39 days) discontinued due to "parent mistrust in child's compliance," coded as "other"

7.1.3.2 Adverse events associated with dropouts from clinical studies

Phase I study

Two children withdrew from this study due to an adverse event. A four year old boy received his dose then required almost 4 hours to fall asleep. He then rested quietly for 2 hours before awakening in an agitated state. He was discharged from the study prior to completion of the scheduled blood draws. He had had 5 mg of zolpidem in the past and had manifested a similar response according to his mother. The investigator felt that this was an expected effect "due to the dose of zolpidem being too low." A 9 year old girl in the 0.25 mg/kg group complained of dizziness 15 minutes after dosing then became anxious. She was released, wide awake, 2 hours after dosing. She fell asleep approximately 4.75 hours after dosing.

Phase III study

[*Reviewer's note: The AE are highlighted with bold font.*]

Placebo treatment arm

There were no discontinuations due to adverse events in this treatment arm other than the one reported above as an SAE.

Zolpidem treatment arm

- Subject 840009002 (exposed 1 day)

This 7 year old male, with no past history of hallucinations, was noted to have **hallucinations**, which began 15 minutes after ingestion of study drug and lasted for 1.75 hours. He had multiple **falls** while hallucinating. He was withdrawn from the study due to these adverse events. The narrative reports that the patient was discontinued due to patient

request-"the patient and parent refused to return for additional visits." It is reasonable to assume that the adverse events described might have affected their decision.

- Subject 840055004 (exposed 1 day)

This 11 year old male complained of **lethargy, 'a burning sensation and restless limbs'** beginning shortly after ingestion of study medication. The adverse events persisted for approximately 1.75 hours. He was taken to the emergency room for evaluation and subsequently withdrawn from the study. He recovered within 48 hours.

- Subject 840045001 (exposed 2 days)

This 11 year old male was noted to have **sleep-walking** and **enuresis** on Day 2. These events occurred 1.75 hours after ingestion of study medication. He had no past history of somnambulism or enuresis. The narrative notes that the patient was taken off of the study due to the parent withdrawing consent. It is reasonable to assume that the adverse events described might have affected that decision.

- Subject 840008011 (exposed 2 days)

This 8 year old male, with no past history of hallucinations, was noted to have **hallucinations**, both hypnogogic and hypnopompic. The narrative notes that the patient was taken off of the study on Day 3 due to poor compliance not due to an adverse event but it is reasonable to assume that the adverse events described might have affected compliance.

- Subject 840015001 (exposed 6 days)

This 7 year old male was noted to have **abdominal pain, vomiting, dizziness** (coded as gastroenteritis) beginning 30 minutes after ingestion of study drug on Day 6. He was evaluated in an emergency room due to his level of discomfort. He was subsequently removed from the study. Prior to being removed from the study, he had complained of **constipation** on Day 5 and **eye swelling** on Day 6.

- Subject 840002037 (exposed 6 days)

This 14 year old male complained of **morning somnolence** on Day 1 of the study. He was removed from the study on Day 6 due to the persistence of this adverse event. The symptom resolved after 8 days.

- Subject 840042007 (exposed 19 days)

This 16 year old male complained of '**retching**' upon attempts to ingest the study medication. This difficulty persisted until Day 19 when he was removed from the study.

- Subject 840051006 (exposed 25 days)

This 8 year old female, with no past history of hallucinations, was reported to have had severe visual **hallucinations** as well as mild **dyspnea and tremor** on Day 24 of the study. On Day 25, she had a second episode of these symptoms as well as new-onset **auditory hallucinations**. She was undergoing a polysomnogram on Day 25 and the symptoms were documented to have lasted for 2 hours and 38 minutes. The investigator referred her to the

hospital emergency room. She was withdrawn from the study due to the adverse events described. Additionally, on Day 8, she had complained of a **headache** which persisted for 19 days.

- Subject 840022012 (exposed 30 days)

This 15 year old boy, with no past history of hallucinations, complained of a **headache**, which lasted for 3 days, beginning on Day 6. On Day 28, he complained of **vomiting and gastroenteritis** which lasted 3 days. On Day 30, approximately 20 minutes after ingestion of study drug, he experienced what were described as severe **hallucinations** lasting 'continuously for 2 hours.' He was evaluated in an emergency room due to the severity of his symptoms. Study drug was discontinued due to this adverse event.

- Subject 840017006 (exposed 45 days)

This 12 year old male complained of difficulty remembering, coded as '**memory impairment,**' on Day 9. This difficulty persisted until Day 27. A **headache** occurred on Day 11. On Day 20, he had an episode of '**affect lability**' which persisted through Day 34. On Day 40, he had another episode of '**affect lability**' which was reportedly more severe than the preceding episode as well as moderate anxiety. These changes in affect began 90 minutes after drug ingestion and persisted until the next morning. Due to this combination of adverse events, he was removed from the study on Day 45.

7.1.3.3 Other significant adverse events

The following adverse events of interest were all coded as non-serious adverse events by the sponsor and were not associated with treatment discontinuation. All of the listed patients had past medical histories which were significant for ADHD and insomnia since those conditions were entry criteria for this study.

7.1.3.3.1 Patients who complained of hallucinations

- Subject 8400017002 (zolpidem)

This 11 year old female was reported to have had 30 minutes of **visual hallucinations** on Day 7 of the study. This adverse event began 1 hour after ingestion of the drug. She had no past history of hallucinations. She also complained of intermittent **dizziness** starting on Day 2 and persisting through Day 11. She completed the study. [*Reviewer's comment: The adverse events described might have been associated with zolpidem ingestion.*]

- Subject 8400380002 (zolpidem)

This 10 year old male was reported to have had 60 minutes of **visual hallucinations** and intermittent **dizziness** on Day 1 of the study. These symptoms persisted through Day 3. He had no past history of hallucinations. On Day 8, he complained of **diarrhea and dizziness.** The latter symptoms lasted 2 days. On Day 35, he began to manifest intermittent **irritability** which was persistent at the end of the study. [*Reviewer's comment: The adverse events described might have been associated with zolpidem ingestion.*]

- Subject 840042009 (zolpidem)

This 11 year old male was reported to have had **hallucinations** as well as **drooling and gait disturbance** on Day 2 of the study. The onset was 45-60 minutes after ingestion of study medication. He recovered within 48 hours. On Day 22, he complained of a second episode of **hallucination** and was noted to have had associated **somnambulism**. The latter symptoms lasted 1 day. [*Reviewer's comment: The adverse events described might have been associated with zolpidem ingestion.*]

- Subject 840054004 (zolpidem)

This 12 year old female was reported to have had a **hypnogogic hallucination**, described as 'a perception of a bright light and a human face/figure in the room,' on Day 22 of the study. She recovered within 24 hours. On Day 50, she had an episode of **somnambulism** lasting less than one hour. She also had had an episode of **gastroenteritis** and **headache** from days 4-6. [*Reviewer's comment: The adverse events described might have been associated with zolpidem ingestion.*]

- Subject 840063007 (zolpidem)

This 9 year old male was reported to have had a **hypnogogic hallucination** on Day 1 of the study. He recovered within 48 hours. On Day 23, he complained of a second episode of **hypnogogic hallucination**. The latter symptoms again lasted 2 days. [*Reviewer's comment: The adverse events described might have been associated with zolpidem ingestion.*]

- Subject 840038001(zolpidem)

This 11 year old male was reported to have had 60 minutes of **visual hallucinations** on Day 1 of the study. On Days 2-4, he had "**disorientation**"; approximately 30 minutes after ingestion of the study medication, he walked in an incorrect direction to the bathroom and urinated in his pants (**loss of bladder control**). On the same days he complained of moderate "**unsteadiness/balance disorder**". On Day 16, he complained of moderate **anxiety** which persisted throughout the study. On Day 29, he complained of a upper respiratory tract infection which lasted for two days. On Day 30, he again complained of **balance disorder** similar to the complaints at the beginning of the treatment period but this time he additionally complained of **dysarthria.** [*Reviewer's comment: All of the adverse events described, with the exception of the upper respiratory tract infection, might have been associated with zolpidem ingestion. The upper respiratory tract infection is unlikely to be related to use of study drug.*]

7.1.3.3.2 Patients who complained of neurological, psychiatric adverse events other than hallucinations

- Subject 840054015 (zolpidem)

This 11 year old male began complaining of mild **diplopia** (which lasted 3 days) and dizziness (which lasted 58 days) starting on Day 1. On Day 19, he complained of a mild **headache** which resolved the same day. On Day 30, he **fell** while running and sustained an **abrasion** on his left forearm. On Day 55, he sustained an **abrasion** on his left leg.

[*Reviewer's comment: The diplopia and the headache might have been related to the use of study drug. The other adverse events reported were not related to study drug.*]

- Subject 840071003 (zolpidem)

This 15 year old male was reported to have moderate symptoms of fatigue upon awakening, which was coded as **malaise,** beginning on Day 2; this symptom persisted throughout the study. On Day 1, he began complaining of mild intermittent **dizziness** after dosing; this also persisted throughout the study. On Day 4 he complained of mild **diarrhea** which lasted for 6 days. On Day 8, he complained of a **headache** which began 40 minutes after dosing with study drug and resolved within 24 hours. He had **sinusitis** on Day 23 which resolved after treatment with azithromycin. On Days 32 and 33, he complained of severe **nightmares.** [*Reviewer's comment: There is a probable association with study drug for the malaise, dizziness, headache and nightmares. All have been the subject of post-marketing reports with this product. The diarrhea and sinusitis were probably not related to study drug.*]

- Subject 840003001 (zolpidem)

This 10 year old male, whose past medical history was notable for headaches, episodic stomachaches, situational anxiety, oppositional defiance and seasonal allergies, was reported to have moderate **emotional lability** on Day 16, coded as "affect lability." This condition persisted for 15 days. Additionally, this patient reported **dizziness** which lasted from Day 1 to Day 18. A **headache** was reported on Day 15. **Viral gastroenteritis** was reported on Day 56, the day after completion of the double-blind treatment period.
[*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an association with study drug for the emotional lability, the headache or the dizziness. The gastroenteritis reported was not related to study drug.*]

- Subject 840002027 (zolpidem)

This 12 year old male was reported to have moderate emotional lability, coded as "**affect lability**" and mild dizziness beginning on Day 1; both symptoms persisted until Day 8. On Day 55, during his final physical examination, he was noted to have a tremor. [*Reviewer's comment: All of the reported adverse events may have been related to study drug.*]

- Subject 840071002 (zolpidem)

This 7 year old male, was reported to have mild morning **affect lability** beginning on Day 11 which was persisting at the end of the study. Throughout the study, the patient complained of **dysgeusia** after ingestion of study medication. On Day 19, he reported **morning somnolence** which persisted through the end of the study. [*Reviewer's comment: All of the reported adverse events may have been related to study drug.*]

- Subject 840010001(zolpidem)

This 14 year old male was reported to have moderate **irritability** on Day 1. This condition persisted for 29 days. Additionally, this patient reported **somnolence** which lasted from Day 1 to Day 16. Intermittent **headache** was reported to last for 29 days. [*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an*

association with study drug for the irritability or the headache. The somnolence may be attributed to use of study medication.]

- Subject 840024001(zolpidem)

This 9 year old male was reported to have **pharyngitis** on day 19, for which he was given analgesic therapy. On Day 53, he was noted to have mild **anxiety**, which persisted throughout the study. On Day 60, he complained of a headache, which persisted until the end of the study. [*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an association with study drug for the anxiety or the headache.*]

- Subject 840007003 (zolpidem)

This 10 year old male was reported to have had mild **word finding difficulty**, which was coded as dysphasia instead of aphasia, on Day 8 of the study; he had intermittent difficulty remembering the names of objects. This aphasia lasted for 18 days. On Day 51, he had a **bicycling accident**, coded as road traffic accident, when he ran over a rock and lost control of his bicycle. He sustained **knee abrasions** as a result of that fall. [*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an association with study drug for his word finding difficulty. Aphasia has been the subject of some post-marketing reports with this product. The bicycle accident is unlikely to be related to use of study drug.*]

- Subject 840051002 (zolpidem)

This 14 year old male was reported to have mild '**bad dreams**' on Day 1 which resolved by Day 5. On Day 12, he began complaining of mild **morning somnolence** which persisted throughout the study. On Day 32, he was noted to be moderately **disoriented**. One hour after ingestion of zolpidem, he was up playing a game and was 'convinced that he was in World War II." This resolved spontaneously. [*Reviewer's comment: All of the adverse events described might have been associated with zolpidem ingestion.*]

- Subject 840071006 (zolpidem)

This 13 year old male was reported to have moderate symptoms of **dizziness** beginning on Day 1; this symptom persisted throughout the study. On Day 5, he began complaining of difficulty remembering events around bedtime beginning approximately 1 hour after dosing, which was coded as moderate **memory impairment,** as well as 'mild **increased dream intensity**.' These two complaints also persisted throughout the study. On Day 7 he complained of mild **clumsiness upon attempts at ambulation** for at least 20 minutes after ingestion of zolpidem; this was coded, inappropriately, as a general disorders and administration site condition. This condition resolved after 15 days on study treatment. Beginning on Day 11 and lasting through Day 52, he was noted to have moderately '**abnormal behavior**,' in the 20 minutes post dosing, specifically defying verbal commands. Moderate myalgia was reported on Day 21 through 27. [*Reviewer's comment: There is a probable association with study drug for the lacunar amnesia, increased dream intensity,*

abnormal behavior and ambulation difficulties. All have been the subject of post-marketing reports with this product.]

- Subject 840069006 (placebo)

This 11 year old male was hospitalized 'due to **impulse-control disorder**' on Day 6; this symptom resolved after 4 days. The narrative notes that in addition to the impulse control disorder, the patients had a **major depressive disorder** as well as **oppositional defiant disorder**. By report, these latter symptoms also resolved within 4 days. On Day 7, he complained of headache and associated emesis. Those symptoms resolved within 24 hours.

- Subject 840051004 (placebo)

This 13 year old male was noted to have **'irritability'** as well as **morning somnolence** on Day 1. These adverse events persisted throughout the study. On Days 11-13, he complained of **rhinorrhea**. Beginning on Day 58, he complained of **bilateral ear pain, nausea and throat pain**. He was subsequently given antibiotic therapy for the latter complaints. [*Reviewer's comment: There is no association with study drug for the adverse events listed.]*

7.1.3.3.3 Other adverse events not listed above

- Subject 840005001 (zolpidem)

This 12 year old male was reported to have had **accidental overdoses** on Days 1 and 2 of the study; he received 12.5 mg of study medication on those evenings instead of 10 mg. For the first 3 days of the study, he reported mild **dizziness** after ingestion of his medication. [*Reviewer's comment: The dizziness may be attributed to use of study medication.*]

- Subject 840054022 (placebo)

This 13 year old male, whose past medical history was notable for right flank hairy nevus, exogenous obesity, headaches and tinea corporis, fell while running on Day 27. His **fall** which was not attributed to disequilibrium resulted in an **abrasion** on his left knee. He had an injury on Day 49 which resulted in an **abrasion** on his right arm. On Day 21 he had an extensive **sunburn** of moderate severity. On Day 57, he had moderate **vomiting**, which was attributed to heat exposure. [*Reviewer's comment: The adverse events reported were not related to study drug.*]

- Subject 840031003 (zolpidem)

This 8 year old male was hit by a lit firework rocket on Day 56 and sustained mild **burn injuries** to his left arm and thorax. From Day 11 through Day 59, he complained of mild **dizziness**. Additionally, mild allergic **rhinitis** was reported on Day 2. [*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an association with study drug for the dizziness. The other adverse events reported were not related to study drug.*]

- Subject 840031005 (zolpidem)

This 11 year old male collided with a relative on Day 12 and sustained a mild **injury,** specifically a **periorbital hematoma**. From Day -2 through Day 18, he was noted to have a

papular rash on his trunk and extremities. [*Reviewer's comment: While there is not a clear causal connection, it is not possible to completely rule out an association with study drug for the rash. The other adverse event reported was not related to study drug.*]

- Subject 840066004 (placebo)

This 8 year old female bumped her head and had local tenderness on Day 19; this was coded as "**head injury**." She recovered from the incident in 27 days. She had **contact dermatitis** noted on Day 6. On Day 44, she was noted to have **vulvovaginitis** and **enterobiasis** (pinworms); both conditions lasted 20 days. On day 63, she reported a mosquito bite on her elbow. [*Reviewer's comment: The adverse events reported were not related to study drug.*]

- Subject 840074013 (placebo)

This 13 year old male, whose past medical history was notable for prematurity, panhypopituitarism and hypothyroidism, was a restrained passenger in a **motor vehicle accident** on Day 22 of the study. He sustained a chest wall contusion as well as a cervical strain injury. On Day 60, he was noted to have **neutropenia**, which the PI did not attribute to use of study medication. This subject completed the entire study. [*Reviewer's comment: The adverse events reported were not related to study drug.*]

- Subject 840074014 (placebo)

This 7 year old male, whose past medical history was notable for asthma, was a restrained passenger in a **motor vehicle accident** on Day 22 of the study. He sustained an ecchymosis on his left arm. This subject completed the entire study. [*Reviewer's comment: This adverse event was not related to study drug.*]

- Subject 840074017 (placebo)

This 7 year old male, whose past medical history was notable for asthma, allergies and excema, was a restrained passenger in a **motor vehicle accident** on Day 1 of the study. He sustained no clinically evident injuries. On Day 2, he was noted to have bilateral **tinea pedis** for which he was treated. This subject completed the entire study. [*Reviewer's comment: The adverse events reported were not related to study drug.*]

- Subject 840074018 (zolpidem)

This 8 year old female was a restrained passenger in a **motor vehicle accident** on Day 1 of the study. She had **epistaxis** as well as an **injury to her left orbit** both of which were attributed to hitting the car window with her face. This subject completed the entire study. [*Reviewer's comment: The adverse events reported were not related to study drug.*]

- Subject 840066002 (zolpidem)

This 7 year old male was reported to have mild symptoms of "lethargy, fainting or lightheadedness" on Day 38, coded as **orthostatic hypotension**. This condition persisted for 1 day. Additionally, this patient reported **eye discharge** on Day 60, which was treated. He recovered in 3 days. [*Reviewer's comment: While there is not a clear causal connection, it is*

not possible to completely rule out an association with study drug for the orthostatic hypotension described. The eye discharge was not related to the use of study medication.]

- Subject 840054007 (zolpidem)

This 6 year old male was reported to have had a **contusion** of his left tibia after falling on a trampoline on Day 7. Additionally, this patient reported a **headache** on Day 39. [*Reviewer's comment: It is not possible to completely rule out an association with study drug for the headache described. The contusion was not related to the use of study medication.*]

- Subject 840022020 (zolpidem)

This 13 year old male was reported to have had a **fall** with resultant **left wrist sprain** on Day 56. [*Reviewer's comment: It is not possible to completely rule out an association with study drug for the fall as described.*]

7.1.4 Other Search Strategies

There were no other search strategies used in the review of this product.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Phase I trial
During the Phase I single dose trials, subjects were assessed at screening and during the course of the trial for adverse events.

Phase III trial
During the Phase III trials, subjects were assessed at screening and at each visit during the course of the trial for adverse events. They were also assessed on Day 63 in the follow-up phase.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Phase I trial
The adverse events appear to have been appropriately categorized with appropriate use of preferred terms.

Phase III trial
While in general, the adverse events appear to have been appropriately categorized with appropriate use of preferred terms, there were exceptions e.g. as noted in section 7.1.3.3.

Additionally Patient 840008011 reported a hypnogogic hallucination which was coded under narcolepsy associated symptoms instead of perception disturbances, which was the high level term used for the other episodes of hallucination reported.

7.1.5.3 Incidence of common adverse events

The adverse event reported with the highest incidence overall during the Phase I single-dose trial was dizziness. The adverse events reported with the highest incidence during the Phase III placebo-controlled trial were dizziness (23.5% in the zolpidem treatment arm, 1.5% in the placebo treatment arm), headache (12.5% in the zolpidem treatment arm, 9.2% in the placebo treatment arm), and hallucinations of various sorts (7.4% in the zolpidem treatment arm, 0% in the placebo treatment arm).

7.1.5.4 Common adverse event tables

Table 4: Common adverse events seen in the Phase III study

Preferred term	Placebo (N=65) n(%)	Zolpidem (N=136) n(%)
Dizziness	1 (1.5)	32 (23.5)
Headache	6 (9.2)	17 (12.5)
Hallucinations (of any sort)	0	10 (7.4%)
Somnolence (morning)	5 (8)	8 (6)
Gastroenteritis (all sorts)	0	6 (4.4)
Diarrhea	1 (1.5)	4 (2.9)
Fall	1 (1.5)	4 (2.9)
Nasopharyngitis	1 (1.5)	4 (2.9)
Affect lability	0	4 (2.9)
Enuresis	0	4 (2.9)
Excoriation	1 (1.5)	3 (2.2)
Injury	1 (1.5)	3 (2.2)
Anxiety	0	3 (2.2)
Diplopia	0	3 (2.2)
Sleepwalking	0	3 (2.2)
Abnormal dreams	0	2 (1.5)
Disorientation	0	2 (1.5)
Drooling	0	2 (1.5)
Dysgeusia	0	2 (1.5)
Otitis media	0	2 (1.5)
Joint sprain	0	2 (1.5)
Memory impairment	0	2 (1.5)
Meningitis (viral)	0	2 (1.5)
Extremity pain	0	2 (1.5)
Pharyngitis (streptococcal)	0	2 (1.5)
Tremor	0	2 (1.5)

Modification of table (9.2.2)2 in the study report for EFC6820, page 78 of 1719

7.1.5.5 Identifying common and drug-related adverse events

The majority of the adverse events reported, as may be seen in the table above, showed a consistent difference from control. Dizziness and hallucinations at a minimum may be considered drug-related.

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were done since the adverse events listed in 7.1.5.5 are well described in the literature on zolpidem.
Next day residual effects were assessed with the Pediatric Daytime Sleepiness Scale, a subjective measure. Rebound insomnia at treatment discontinuation was measured by actigraphy, an objective measure.

7.1.6 Less Common Adverse Events

In the pediatric population, there appears to be a clear association between ingestion of active drug and hallucinations of various sorts, with a consistent difference seen between the active and placebo treatment arms.

While a consistent difference from control across doses and across study populations was not seen in the phase I or III trials in the adult population, hallucinations (visual and auditory) have been described as an associated adverse event with this product in both pre-marketing trials and in post-marketing reports.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Phase I trial
The protocol for the Phase I studies required laboratory testing as a baseline and at the follow-up visit. No patterns of clinically significant findings were noted.

Phase III trial
The protocol for the Phase III study, EFC 6820, required laboratory testing of blood chemistry and hematological parameters during screening in order to determine eligibility. There was follow up testing at Week 8.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The Phase III study was chosen for analysis since it provided information about patients who used the product as it might be expected to be used in the real world.

Pooling was not done since the studies used different dose levels.

7.1.7.3 Standard analyses and explorations of laboratory data

A review of the liver function tests, the metabolic functions, the renal function tests and the hematological parameters did not reveal any clinically significant changes.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Phase I trials
Vital signs were examined at screening, on the day of study drug administration and at the termination visit. No clinically significant findings were noted in the study participants.

Phase III trial
In the Phase III study vital signs were examined at screening, at week 8 and during the follow-up phase.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The Phase III study was chosen for analysis since it provided information about patients who used the product as it might be expected to be used in the real world.

Pooling was not done since the studies used different dose levels.

7.1.8.3 Standard analyses and explorations of vital signs data

A review of the vital signs changes from baseline to last on-treatment value did not reveal any clinically significant changes.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Phase I and Phase III trials
The protocols for these studies did not include ECGs.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This section is not relevant for this review.

7.1.9.3 Standard analyses and explorations of ECG data

This section is not relevant for this review.

7.1.9.4 Additional analyses and explorations

This section is not relevant for this review.

7.1.10 Immunogenicity

There was no immunogenicity data provided to assess the impact of immunogenicity on safety, efficacy, clinical pharmacokinetics or pharmacology.

7.1.11 Human Carcinogenicity

The following text is taken directly from the currently approved label for Ambien:

> "Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m2 basis, respectively. No evidence of carcinogenic potential was observed in mice.
>
> Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.
>
> Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in

cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice."

7.1.12 Special Safety Studies

Residual effects were assessed through use of the pediatric daytime sleepiness scale (PDSS). No significant next-day residual effects were seen.

Table 5: Change from baseline for PDSS

	Placebo (N=65)	Zolpidem (N=136)
Baseline and post-baseline Number	65	132
Baseline Mean (SD) Median Min;Max	19.8 (5.0) 20.0 8; 29	19.6 (5.0) 20.0 7; 31
Change from baseline LS Mean (SE) LS Mean Difference (SE) 95% CI p-value vs Placebo	-3.2 (0.78) - - -	-5.0 (0.55) -1.8 (0.95) (-3.70 to 0.05) 0.0567

Note: PDSS is a 8 items scale with 5 categories raging from 0 (never) to 4 (always)
Note: p-values come from analysis of covariance using age and treatment as fixed effect and baseline as covariate
Copy of table (9.6.1)1 from the study report for EFC 6820

7.1.12.1 Assessment of drug rebound effect

Actigraphy was used to evaluate latency to persistent sleep after treatment discontinuation. No significant rebound was detected.

Table 6:

		Placebo (N=65)	Zolpidem (N=136)
Night 1	Baseline and post baseline Number	28	80
	Baseline		
	Mean (SD)	67:26 (38:05)	67:11 (50:20)
	Median	63:00	54:00
	Min;Max	7:00; 142:00	5:00; 318:00
	Change from baseline		
	LS Mean (SE)	16:05 (17:07)	31:55 (10:01)
	LS Mean Difference (SE)	-	15:50 (19:49)
	95% CI	-	(-23:27 to 55:08)
	p-value vs Placebo	-	0.4260
Night 2	Baseline and post baseline Number	33	77
	Baseline		
	Mean (SD)	67:29 (37:15)	69:27 (52:52)
	Median	64:00	55:00
	Min;Max	3:00; 142:00	5:00; 318:00
	Change from baseline		
	LS Mean (SE)	11:18 (12:51)	6:26 (8:25)
	LS Mean Difference (SE)	-	-4:52 (15:23)
	95% CI	-	(-35:22 to 25:38)
	p-value vs Placebo	-	0.7527

Note : p-values come from analysis of covariance using age and treatment as fixed effect and baseline as covariate
Copy of table (9.6.2.2)1 from the study report for EFC 6820

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Zolpidem tartrate is a class IV controlled substance.

7.1.14 Human Reproduction and Pregnancy Data

The following is from the approved labeling for Ambien:

"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 embryofetal toxicity was 4 mg base/kg/day (between 4 to 5 times the MRHD of Ambien on a mg/m2 basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (over 35 times the MRHD of Ambien on a mg/m2 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 toxicity was below 1 mg base/kg/day (< 2-times the MRHD of Ambien on a mg/m2 basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day (between 9 and 10 times the MRHD of Ambien on a mg/m2 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 on 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 (between 4 to 5 times the MRHD of Ambien on a mg/m2 basis).

There are no adequate and well-controlled studies in pregnant women. Ambien 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. 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.

Ambien (zolpidem tartrate) has no established use in labor and delivery

Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6± 0.3 hr). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m2.

The use of Ambien in nursing mothers is not recommended."

7.1.15 Assessment of Effect on Growth

The effect on height was not evaluated and would not have been expected to be affected in a 2 month study. There was no significant change in weight.

7.1.16 Overdose Experience

There were no reported instances of drug overdose with this formulation during the clinical studies.

The currently approved label for Ambien notes that zolpidem's sedative hypnotic effect may be reversed by administration of flumazenil.

7.1.17 Postmarketing Experience

Zolpidem has been and is currently being marketed as both an immediate release formulation and a modified release formulation. A discussion of the available postmarketing information may be found in section 7.2.2.2 of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration from studies EFC 8749 and EFC 6820

Table 7 : Study type and populations

Study Number	Design	Dosing schedule
EFC 4529	DB, R	Single-dose
EFC 6820	DB, R, PC, PG	2 months of fixed-dose double-blind treatment

7.2.1.2 Demographics

The Phase I study enrolled 67 patients, 48 of whom were White (72 %). The demographic data from the Phase III study may be seen in the table below.

Table 8 : Demographics in Phase III study

Protocol #	n	M/F	Ethnicity	
EFC 6820	201	155M/46F	White	165 (82.1%)
			Black	31 (15.4%)
			Native Hawaiian or pacific islander	1(<1%)
			American Indian or Alaska Native	1(<1%)
			Other	3 (1.5%)

7.2.1.3 Extent of exposure (dose/duration)

All patients in the Phase I study received a single dose of study medication. The exposure during the Phase III study may be seen below.

Table 9 : Exposure during Phase III study: EFC 6820

		Placebo (N=65)	Zolpidem (N=136)
Duration of exposure (days)	Number	65	136
	Mean (SD)	52 (12)	51 (14)
	Median	56	56
	Min ; Max	7 ; 62	1 ; 61
Duration of exposure (days) [n(%)]	1 to 7 days	1 (1.5)	9 (6.6)
	8 to 14 days	2 (3.1)	0 (0)
	15 to 21 days	2 (3.1)	1 (0.7)
	22 to 28 days	1 (1.5)	1 (0.7)
	29 to 42 days	0 (0)	2 (1.5)
	43 to 56 days	40 (61.5)	92 (67.6)
	> 56 days	19 (29.2)	31 (22.8)
Patient exposed at least 8 weeks		52 (80.0)	111 (81.6)

Copied from the study report for EFC6820, table (9.1)1 on page 75

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no other studies in pediatric patients used to evaluate safety for this review.

The sponsor provided synopses of 6 additional pediatric studies:

Study 87-000692:
This was a Phase I randomized, double-blind, single-dose, parallel-group, placebo-controlled trial entitled "Nocturnal pharmacokinetics of zolpidem in children." This study, which was conducted in France, enrolled and treated 12 children aged 6-14 who had growth delay and were being evaluated for nocturnal secretion of growth hormone. The zolpidem-related assessments were done concurrent with the assessments of growth hormone. According to the synopsis, "one subject (zolpidem 10 mg) reported an AE during this study. One hour after dosing, she experienced a floating sensation as if she was lying in a hammock. She also thought that she had been moved to another room. The sensations were not unpleasant and lasted 45 minutes. No corrective treatment was initiated. The AE was considered by the investigator to be related to the investigational product."

Study 88-00522:
This was a randomized, active-control study with 4 parallel-groups entitled "Study of zolpidem and diazepam as oral pre-medication for children prior to general anesthesia." This study, which was conducted in France, treated 199 children, aged 4 to 16 years, who were hospitalized for surgical procedures. The doses ranged from 2.5 mg to 20 mg. The sponsor reports that for "the AEs of nausea and/or vomiting, children who received zolpidem suffered more from vomiting

than did children who received diazepam only at the 60 minutes time-point (p=0.004). Some patients suffered transient visual disorders, usually reported as episodes of diplopia, these were observed more frequently in the zolpidem group (17/99) than the diazepam group (2/100).

Study 95-00874:
This was a Phase I study entitled "Comparative, double-blind study of the sedative activity of zolpidem in neonates following a single intravenous dose-safety report." This study, which was conducted in France, treated 2 neonates. The subjects both received placebo. The study was discontinued by the sponsor "for internal reasons, which were not related to the safety or efficacy results of the study."

Study 85-00441:
This was a Phase I study entitled "A study of zolpidem in oral pre-medication prior to general anesthesia in children." This open-label study, which was conducted in France, treated 11 children, who were hospitalized for a surgical procedure. The first 5 subjects received 5 mg and the remaining subjects received 10 mg. The sponsor reports "2 subjects in the zolpidem 5-mg group experienced temporary disorientation and excitation. Two subjects in the zolpidem 5-mg group also experienced tracheal hypersecretion and 1 of these subjects had moderate obstruction of the respiratory tract."

Study 88-00179:
This was a Phase II study entitled "Study of zolpidem in sleep induction in children." This open-label study, which was conducted in France, treated 20 children, aged 5 to 15 years, "with transient disorders of sleep associated with living conditions in an institution." The doses ranged from 2.5 to 15 mg. The sponsor reports two episodes of vomiting (5 mg, 7.5 mg) but no other adverse events.

Study 90-00136:
This was a study entitled "Zolpidem as oral premedicant in children before follow-up esopho-gastro-duodenoscopy: An open-pilot study of efficacy and pharmacokinetics." This open-label study, which was conducted in Italy, treated 10 children, who were hospitalized for surgical procedures. The doses ranged from 0.2mg/kg to 0.6 mg/kg. The sponsor reports that the "trial was discontinued after the enrollment of 10 patients, due to lack of efficacy and the occurrence of disturbing 'oneiroid' states after zolpidem administration. Five of the 10 patients experienced AEs at most dose levels which included oneiric state (4/10), diplopia (3/10), agitation (2/10) anxiety (2/10) and vertigo (1/10)."

7.2.2.2 Postmarketing experience

The sponsor provided a review of the postmarketing data from spontaneous reports of zolpidem used in patients under 17 years old. In the period from March 1988 through June 2006, they found 158 reports in their pharmacovigilence database. The majority of the cases were coded as nervous system (45) or psychiatric disorders (77). The more notable findings are summarized below.

- In the children aged 5 or younger, there was one death which was a suspected infanticide (4 year old boy). There were 13 reports of somnolence as well as 3 reports of hallucination and 1 report of psychosis. The latter was a 5.5 year old boy who was receiving methylphenidate and zolpidem (0.25 mg/kg/day). After two days of treatment he began hallucinating and became agitated, violent and disoriented. Six hours later he reported transient blindness. The total number of cases in this age group was 24.
- In the children aged 6 to 11 years, there were 4 reports of somnolence and 1 report of anterograde amnesia as well as 3 reports of hallucination. There was one death which was a 6 year old boy who drowned. His stepmother stated that she had administered a dose of zolpidem to the child 6 months earlier and that zolpidem had been self-administered zolpidem the day before he died. Forensic analysis revealed that the zolpidem intake had been ongoing for months and was not sporadic as was reported. The total number of cases in this age group was 13.
- In the children aged 12 to 17 years, there were 21 reports of somnolence/depressed level of consciousness, 1 report of anterograde amnesia, 12 reports of confusion, 15 reports of agitation, 1 episode of psychosis and 1 episode of suicidal ideation as well as 40 reports of hallucination. The total number of cases in this age group was 121.

In order to assess the adult/elderly post marketing experience for zolpidem in the immediate release formulation, I reviewed the periodic safety update reports submitted to the Ambien NDA (#19-908) for the period from 16 December 2002 through 15 December 2004. The finding of perhaps the greatest clinical significance was the number of reports (n=42) of hallucinations, predominantly visual although tactile and auditory hallucinations were also described. I observe that most of these spontaneous reports came from people who took ≥2 times the recommended dose for age. This observation would lead me to postulate that there may be a dose-response relationship: If the medicine is taken at ≥2 times the recommended dose for age, the risk of hallucination increases. We know from the controlled studies that there is a baseline risk of hallucination, even when taking the recommended dose.

7.2.2.3 Literature

The sponsor provided an adequate selection of references from the sleep literature for this review. The references were provided as *pdf* files with hotlinks in different sections of the application.

7.2.3 Adequacy of Overall Clinical Experience

In addition to the data accrued during drug development, the agency has amassed post-marketing data on zolpidem since the approval of Ambien on 16 December 1992.

The placebo-controlled trial performed was adequate to assess the question of drug effect on sleep latency (the primary objective).

This application exposed an adequate number of subjects. The gender ratio was appropriate, reflecting the skewed distribution of ADHD diagnoses in the population. While it may have been

desirable to achieve greater ethnic diversity in the population studies, that is a problem endemic to clinical trials and not specific to this development program. Overall the inclusion exclusion criteria were appropriate. The dose and durations of exposure were adequate to assess safety for short-term use of this product.

The sponsor appropriately evaluated participants for next-day residual and rebound effects, both of which have been associated with use of the sedative/hypnotics.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was new preclinical data provided for review in support of this submission.

7.2.5 Adequacy of Routine Clinical Testing

The methods that the sponsor used for routine clinical testing were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The information on zolpidem tartrate metabolism, clearance and drug-drug interaction comes primarily from pre- and post-marketing experience with Ambien. The currently approved Ambien label contains information on the enzymatic pathways responsible for drug clearance. The sponsor has included information on significant drug-drug interactions for drugs such as digoxin, fluoxetine, rifampin and itraconazole in the label.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The class specific adverse events of concern are the next-day residual effects and the rebound effect after abrupt drug discontinuation. The sponsor adequately assessed the study participants for these effects as detailed in section 7.1.12. In summary, there was no next-day residual effect seen. Rebound effects were not significant.

7.2.8 Assessment of Quality and Completeness of Data

The data provided appears to be complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

There were no relevant additional submissions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In pediatric patients, Zolpidem is capable of producing neuropsychiatric adverse effects such as hallucinations, headache and dizziness.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

I did not pool the data across the submitted studies.

The safety data for the individual studies has been presented earlier in this section.

7.4.1.2 Combining data

The data was not combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only a single dose was tested so it is not possible to determine whether there is a dose dependency for adverse findings.

7.4.2.2 Explorations for time dependency for adverse findings

The efficacy trial performed in support of this NDA lasted for a total of two months. There were no clear examples of time-dependent adverse events.

7.4.2.3 Explorations for drug-demographic interactions

The susceptibility to adverse effects of sedative/hypnotic agents is known to correlate with age in adults. The only potential age-related associated adverse event was hallucinations, which were seen more frequently in patients under 11 years.

7.4.2.4 Explorations for drug-disease interactions

This submission did not contain sufficient information on concomitant diseases to allow meaningful explorations for drug-disease interactions. Although not assessed during this

development program, the approved labeling for Ambien notes that this product should be used with caution in patients with compromised respiratory function. The label also states that no dosage adjustment is needed in patients with renal dysfunction though reduced doses should be used in persons with hepatic dysfunction.

7.4.2.5 Explorations for drug-drug interactions

The sponsor did not evaluate for drug-drug interaction during this Phase 3 study.

7.4.3 Causality Determination

In the pediatric population, Ambien is capable of producing the following adverse effects:

- Hallucinations
- Dizziness
- Headache
- Sleepwalking
- Abnormal dreams
- Memory impairment

Episodes of dizziness and headache were reported in both the placebo and the zolpidem group, albeit at different rates. There were no reports of hallucinations, sleepwalking, abnormal dreams or memory impairment in the placebo group; all such reports came from the zolpidem group.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Due to the elevated risk of CNS-related adverse events and the apparent absence of therapeutic benefit, there is no appropriate dosing regimen in the pediatric population.

8.2 Drug-Drug Interactions

The information on zolpidem tartrate metabolism, clearance and drug-drug interaction comes primarily from pre- and post-marketing experience with Ambien. The currently approved Ambien label contains information on the enzymatic pathways responsible for drug clearance. The sponsor has included information on significant drug-drug interactions for drugs such as digoxin, fluoxetine, rifampin and itraconazole in the label.

8.3 Special Populations

Gender

The sponsor reported, on page 80 of the study report for EFC6820, that the "combined incidence of dizziness, headache, hallucinations was slightly higher in males [53 of 155 (34.2%)] compared with females [14 of 46 (30.4%)]."

In Table (13.4.1)3 of the study report for EFC6820 which summarizes the treatment emergent adverse events by gender, one can see that the rate of any AE for males is slightly higher in the zolpidem group (64.8%) than the placebo group (55.3). The rate in zolpidem treated females, 53.6%, is just under twice that in the placebo group (27.8%).

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

8.4 Pediatrics

This study was designed to evaluate Ambien for use in children.

8.5 Advisory Committee Meeting

The Agency did not convene an advisory committee meeting to discuss the current study.

8.6 Literature Review

A comprehensive literature review was not done for this efficacy supplement.

8.7 Postmarketing Risk Management Plan

There was no postmarketing risk management plan submitted for this product.

8.8 Other Relevant Materials

There were no other relevant materials reviewed for this submission.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
The submitted efficacy study did not demonstrate efficacy in the pediatric population.

Safety
There are safety concerns about the use of this product 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%). It is not inconceivable that hallucinatory experiences at bedtime might cause a

fear-based reluctance to go to sleep and further exacerbate the baseline insomnia in susceptible pediatric patients.

(b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no recommended risk management activity for this product.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this product.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests for this product.

9.4 Labeling Review

Changes were made to the following sections of the label:
1 INDICATIONS AND USAGE
5.5 Special Populations
8.4 Pediatric use
17 Patient Counseling Information

9.5 Comments to Applicant

Changes were made to the following sections of the label:
1 INDICATIONS AND USAGE
5.5 Special Populations
8.4 Pediatric use
17 Patient Counseling Information

You have previously been informed of changes to the warnings section regarding complex sleep behaviors (see agency letter of 12/06). The class-labeling language should be added to this label.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Efficacy, safety and tolerability of zolpidem in the treatment of children aged 6-17 years with attention-deficit/hyperactivity disorder-associated insomnia: A multi-center, randomized, double-blind, placebo-controlled study: EFC6820

10.1.1.1 Objectives

Primary

- To evaluate the hypnotic efficacy of 0.25 mg/kg/day (with a maximum dose of 10 mg/day) of zolpidem compared with placebo in children aged 6-17 years (inclusive) experiencing ADHD-associated insomnia

Secondary

- To evaluate the clinical and biological safety of 0.25 mg/kg/day (with a maximum of 10 mg/day) of zolpidem in children with ADHD-associated insomnia
- To evaluate the potential for next-day residual effects and for rebound insomnia after treatment discontinuation of zolpidem in children with ADHD associated insomnia
- To evaluate the consequences of the treatment of insomnia on behavioral and cognitive components of ADHD

10.1.1.2 Study design

This was to be a multi-center, double-blind, placebo-controlled, randomized (2:1), parallel-group, fixed-dose trial.

10.1.1.3 Study population and procedures

10.1.1.3.1 Study duration

12 weeks comprising three segments

- Segment A: up to 21 days without study medication
- Segment B: an 8-week double-blind treatment phase,
- Segment C: 7-day follow-up phase with no study medication

10.1.1.3.2 Entry criteria

Inclusion criteria:

- Male or female between 6 and 17 years old, inclusive

- Children with ADHD as defined by DSM-IV-TR criteria
- A complaint of childhood insomnia defined as repeated difficulty with sleep initiation or consolidation that occurs despite adequate age appropriate time and opportunity for sleep. The existence of sleep difficulty was to be supported by statements from the child and/or caregiver that sleep is not properly initiated or maintained.
- Baseline PSG must reveal > 30 minutes latency to persistent sleep (LPS).
- Sleep disturbance must not have been attributable to either the direct physiologic effect of a drug of abuse or misuse of a prescribed medication
- Subject should have been stabilized on all long-term medication therapy, including ADHD treatment, for at least one month prior to study entry
- If a female of childbearing potential, the subject must have had a confirmed negative pregnancy test prior to randomization and have been using a recognized effective method of birth control as defined within the protocol. Abstinence was considered an acceptable method of birth control for this study. [Amendment 01 clarified that childbearing potential was to be determined by the initiation of menses.]
- Written consent must have been obtained from the parent/legal guardian
- Written assent must have been obtained from pediatric patients of the appropriate age who are capable of giving assent as determined by parent/legal guardian. The process was to be IRB approved.

Exclusion criteria:

- Mental retardation
- Autism spectrum disorder
- A history of sleep apnea or evidence of sleep apnea on screening/baseline PSG
- Periodic limb movement > 5/hr as demonstrated on screening/baseline PSG
- A history of bipolar disorder, major depression, conduct disorder, or generalized anxiety disorder (other than obsessive-compulsive disorder) as determined by clinical interview and DSM-IV-TR criteria.
- The presence of any untreated or uncompensated clinically significant renal, endocrine, gastrointestinal, hepatic, respiratory, cardiovascular, neurological (excluding ADHD), hematological, immunologic, cerebrovascular disease or malignancy.
- Elevations of renal and/or liver function tests on screening blood > 2 times the upper limit of normal for age.
- Substance abuse or dependence
- Known hypersensitivity to zolpidem or previous adverse experience with zolpidem
- Pregnancy or lactation
- Current participation in another clinical trial
- Subject's refrigerator is not large enough for a medication lock box
- Parent/guardian or subject does not speak or understand English
- Parent/guardian or subject is not capable of completing the study
- [Amendment 01 added current treatment with rifampicin or sertraline as an exclusion criterion.]

10.1.1.3.3 Study medications

Study medications: Zolpidem liquid (2.5 mg/ml)
Placebo

Patients were to receive study medication dosed at 0.25 mg/kg of body weight (maximum dose of 10 mg) to be taken nightly 30 minutes before their usual bedtime.

10.1.1.3.4 Study procedures

Screening period (visit 1):
During this phase, careful screening will be done including a history of sleep habits/disturbances. An appropriate sleep schedule for the child will be established once the parents/guardians have been instructed on good sleep hygiene practices. Polysomnographic testing and actigraphy testing will be performed and the results will inform eligibility.

Special evaluations to be done during this phase include completion of an ADHD DSM-IV checklist and laboratory testing. Concomitant medications will be documented including dose and dosing schedule.

The date of the next visit as well as the date of polysomnography (PSG) and actigraphy testing will be established.

Baseline Visit (Visit 2):
The PSG sleep diary and actigraphy data, done after Visit 1, will be reviewed and subject eligibility will be determined.

At this visit clinical global impressions (limited to illness severity) will be collected from the child and from the parent/legal guardian.

The Conner's ADHD rating scale, the school tardiness/attendance record, the Conner's continuous performance test II (CPT-II), and the pediatric daytime sleepiness scale will be completed.

The family will be given study medication with instructions for dosing.

Treatment Phase:
Month 1-Visits 3, 4, 5 and 6
At these weekly visits clinical global impressions will be collected from the child and from the parent/legal guardian. The Conner's ADHD rating scale, the school tardiness/attendance record and the pediatric daytime sleepiness scale will be assessed at each visit. Actigraphy data and the Conner's continuous performance test II (CPT-II) will be collected at Visit 6 (week 4) only.

The on-treatment polysomnography testing is to be done between visits 5 and 6 if possible. If that is not possible, the PSG testing should be done between Visits 6 and 7. Actigraphy data should be collected during the same treatment period as the PSG testing.

Month 2-Visits 7 and 8
At these biweekly visits (weeks 6 and 8) clinical global impressions will be collected from the child and from the parent/legal guardian. The Conner's ADHD rating scale, the school tardiness/attendance record and the pediatric daytime sleepiness scale will be assessed at each visit.

At visit 8, the actigraphy monitor should be dispensed with instructions for use during the first two nights after treatment discontinuation. The Conner's continuous performance test II (CPT-II) will be collected at this visit.

End of study/discontinuation-Visit 9
The actigraphy data from the two nights after discontinuation will be collected. Clinical global impressions will be collected from the child and from the parent/legal guardian. The Conner's ADHD rating scale, the Conner's continuous performance test II (CPT-II), and the pediatric daytime sleepiness scale will be completed. At this visit an end-of-study history and physical examination will be obtained.

Concomitant therapy:
"All concomitant therapy deemed necessary by the Investigator and not specifically disallowed by the protocol will be permitted at the discretion of the investigator."

Prescription and non-prescription sedative drugs given for the purpose of sleep induction given for the purpose of sleep induction are not allowed. The protocol specifically lists "hypnotics, melatonin, herbal products, antihistamines and other sleep aids including clonidine."

10.1.1.3.5 Efficacy parameters
The primary efficacy measure was to be latency to persistent sleep (LPS) as measured by polysomnography. Polysomnography was to be performed twice: once during segment A (the baseline period) and once during segment B (between weeks 3 and 4).

The secondary measures were to include:
Sleep variables
- Clinical Global Impression, severity-child
- Clinical Global Impression, global improvement-child
- Clinical Global Impression, severity-parent/caregiver
- Clinical Global Impression, global improvement-parent/caregiver
- Actigraphic measures of LPS and TST
- PSG determined Wake time after sleep onset (WASO), number of awakenings after sleep onset (NAASO), and TST

Behavioral variables
- Conner's ADHD rating scale
- School tardiness/attendance reports

Cognitive variables
- Conner's Continuous performance Test II (CPT-II)

Safety assessments

- Adverse events
- Physical examinations including vital signs
- Laboratory (hematological, chemistry, urinalysis) findings and reports
- Pediatric Daytime Sleepiness Scale (PDSS)
- Actigraphic evaluation of rebound insomnia at treatment discontinuation

10.1.1.3.6 Statistical analysis

The sponsor calculated an overall power of 50% (12 minutes) to 90% (20 minutes). The power analysis used a 15 to 20-minute difference in mean LPS. The study was planned to include 189 patients in order to account for a drop-out rate of approximately 20% and still exposed a minimum of 100 patients to zolpidem for 8 weeks.

Two populations were to be considered:

- The total treated population consisting of all subjects who were randomized and took at least one dose of double-blind study medication during segment B will be used for the safety evaluation.
- The primary efficacy population is the intent-to-treat population comprising all randomized subjects.

Data was to be analyzed as observed without replacement of missing data. Patients who withdrew from the study before completing Segment B for a reason other than loss to follow-up were to have their lass assessment entered as visit 8 on the case report form. The change from baseline in LPS in the ITT population was to be analyzed using an ANCOVA model with treatment group, age group and baseline value (Visit 1) as covariate.

Proposed interim analysis:
The sponsor proposed an interim analysis for efficacy when 50 to 70% of the patients were enrolled, with an alpha level of 1%. A futility analysis was to be conducted concurrently.

Reasons for premature study discontinuation or premature close-out of a center:

- The information gained on the product leads to doubt as to the benefit/risk ratio
- Failure to enroll patients at a given site
- In the event of a breach by the investigator of a fundamental obligation under this agreement
- If the total number of patients are enrolled earlier than expected

10.1.1.3.7 Protocol amendments

The initial protocol incorporated Amendment 1. The major changes are noted above within the inclusion criteria.
The protocol was amended for a second time on 31 March 2006. In addition to minor typographical changes, the following major changes were made:

- The ADHD rating scale IV was to be used as an evaluation tool. The protocol had erroneously referred to this as a Connors scale.

- Canada was added as a participating country and the number of investigational sites was increased to 90 from 50.
- The apnea/hypopnea index was added to clarify sleep apnea determinations.
- The duration of polysomnography recording was clarified to be age dependent:
  6-8 years 11 hours
  9-11 years 10 hours
  12-14 years 9 hours
  15-17 years 8 hours

The protocol was amended for a third time on 07 July 2006. This amendment cancelled the originally planned interim efficacy analysis.

10.1.1.4 Study results

10.1.1.4.1 Trial characteristics

This study began enrolling subjects on 02 March 2006. The last patient completed the study on 10 August 2006. The participating study centers were in the United States of America and Canada. A total of 201 patients were enrolled and randomized; 178 completed the study.

10.1.1.4.2 Demographics

Table : Demographics

	Placebo (n=65)	**Zolpidem (n=136)**	**All (n=201)**
Age (years)			
Mean (SD)	11.1 (2.9)	11.1 (2.7)	11.1 (2.8)
[12-17 years]	27 (41.5%)	63 (46.3%)	90 (44.8%)
[6-11 years]	38 (58.5%)	73 (53.7%)	111 (55.2%)
Sex			
Female	47 (27.7%)	28 (20.6%)	46 (22.9%)
Male	18 (72.3%)	108 (79.4%)	155 (77.1%)
Ethnicity			
White	55 (84.6%)	110(80.9%)	165 (82.1%)
Black	9 (13.8%)	22(16.2%)	31 (15.4%)
Asian	0	0	0
Native Hawaiian or other Pacific islander	0	1	1(<1%)
American Indian or Alaska native	0	1	1(<1%)
Other	1 (1.5%)	2(1.5%)	3 (1.5%)

Each participant provided an ADHD history at the baseline visit. There were no significant differences between the treatment groups in the time from ADHD diagnosis, the ADHD Rating Scale IV total score or the time from diagnosis of insomnia. The percentage of patients who had had behavioral intervention was the similar in the treatment groups though the mean (median) trial of intervention was longer in the placebo group, 30.95 (24) months as compared to the zolpidem group, 20.49 (16) months. The sleep history for each participant was taken at screening

with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, number of awakenings during sleep and wake time after sleep onset. There were no significant differences between the treatment groups when the use of concomitant medications was reviewed.

Twenty-three subjects discontinued prematurely. Eight of the premature discontinuations were in the placebo group:

- Subject 840022022 (exposed 13 days) discontinued at the subject's request due to a family emergency which prevented continuing in the study
- Subject 840006010 (exposed 45 days) discontinued at the subject's request due to an extended time out of town and inability to return to the study site
- Subject 840003013 (exposed 16 days) discontinued at the subject's request due to withdrawn consent when the mother got a new job
- Subject 840011005 (exposed 14 days) discontinued at the subject's request due to parent's refusal to return child to the study site
- Subject 840066008 (exposed 19 days) discontinued at the subject's request due to time constraints
- Subject 840069008 (exposed 7 days) discontinued at the subject's request due to "mom too busy"
- Subject 840002013 (exposed 62 days) discontinued at the subject's request: subject never returned to the study site
- Subject 840002029 (exposed 28 days) discontinued at the subject's request: subject never returned to the study site

Fifteen of the discontinuations were in the zolpidem group. Of the 136 zolpidem treated patients, 121 completed the study; 111 of whom completed at least 8 weeks of treatment.

- Subject 840001009 (exposed 7 days) discontinued due to lack of efficacy
- Subject 840002028 (exposed 49 days) discontinued due to lack of efficacy
- Subject 840030002 (exposed 7 days) discontinued due to lack of efficacy
- Subject 840030009 (exposed 6 days) discontinued due to lack of efficacy
- Subject 840022012 (exposed 30 days) discontinued due to an adverse event
- Subject 840009002 (exposed 1 day) discontinued due to an adverse event
- Subject 840017006 (exposed 45 days) discontinued due to an adverse event
- Subject 840042007 (exposed 19 days) discontinued due to an adverse event
- Subject 840002037 (exposed 6 days) discontinued due to an adverse event
- Subject 840045001 (exposed 2 days) discontinued due to an adverse event
- Subject 840015001 (exposed 6 days) discontinued due to an adverse event
- Subject 840051006 (exposed 25 days) discontinued due to an adverse event
- Subject 840055004 (exposed 1 day) discontinued due to an adverse event
- Subject 840008011 (exposed 2 days) was discontinued due to poor compliance to protocol
- Subject 840001020 (exposed 39 days) discontinued due to "parent mistrust in child's compliance," coded as "other"

10.1.1.4.3 Protocol violations

No patients were removed from the study due to protocol violations.

10.1.1.4.4 Efficacy endpoints

Primary endpoint

This study failed to achieve a statistically significant result on the primary endpoint. The efficacy findings were discussed in detail in section 6 of this review.

Secondary Endpoints

The statistical analysis plan (SAP) for this protocol specified a hierarchical procedure for the statistical analysis. Since the study failed on the primary endpoint, the secondary endpoints were not considered significant.

- Clinical Global Impression, severity-child

At week 4 participants in the active treatment arm reported a greater mean decrease in insomnia severity as compared to the placebo arm. By week 8, a lessening of insomnia severity was only apparent in the older age group.

- Clinical Global Impression, global improvement-child

At weeks 4 and 8, while an improvement in the mean values was noted in the 12-17 year olds treated with active drug as compared to those treated with placebo, this effect was not seen in the 6-11 year olds. There was no difference in the mean values for the latter group.

- Clinical Global Impression, severity-parent/caregiver

At week 4, a lessening of severity was noted in the 12-17 year olds treated with active drug as compared to those treated with placebo; this effect was not seen in the 6-11 year olds. There was no difference in the mean values for the latter group.

- Clinical Global Impression, global improvement-parent/caregiver

At week 4, an improvement in the mean values was noted in the 12-17 year olds treated with active drug as compared to those treated with placebo; this effect was not seen in the 6-11 year olds. There was no difference in the mean values for the latter group.

- Wake time after sleep onset (WASO) assessed by PSG
- Number of awakenings after sleep onset (NAASO) assessed by PSG
- Total Sleep Time (TST) assessed by PSG

There were no significant differences in the change from baseline at Week 4 upon evaluation of any of these parameters between the two groups.

- Actigraphic measures of LPS and TST

There were no significant differences between the treatment arms in either of these measures at week 4.

- ADHD rating scale-IV

When assessed at weeks 4 and 8, there were no significant differences in the baseline-adjusted mean change for either treatment arm.

- School tardiness/attendance reports

This data was confounded by the summer vacation period so no significant conclusions could be drawn.

- Conner's Continuous performance Test II (CPT-II)

When assessments were made at Weeks 4 and 8, there was no significant difference between the treatment arms in the number of omission and commission errors.

10.1.1.4.5 Safety endpoints

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.1.1.5 Reviewer's summary

In my original review of this protocol dated 9 March 2006, I had the following comments for the sponsor:

1. The sleep disturbance must not be attributable to either the direct physiologic effect of a drug of abuse or misuse of a prescribed medication. We must know the time of last stimulant dose (where applicable) administered each day since stimulant use could effect the LPS.
2. We remind you that the PWR specifically states that parents must be asked if behavioral intervention for the child's insomnia has been attempted and for how long the trial (if any) of behavioral intervention went on. The responses should be documented as part of the CRF and reported as part of the background demographic data.
3. You state that expected adverse events are listed in table (6.4) 1 of the Investigator's brochure and unexpected adverse events are to be reported as appropriate. You have not provided us with a copy of the Investigator's brochure. Please do so as soon as possible.
4. Regarding the interim analysis, while it is understandable that you would wish to stop the study if Ambien is found to be futile in the treatment of pediatric insomnia, we would consider safety and efficacy in determining whether this product may appropriately be used in the pediatric population. We require the safety data, preferably from a placebo-controlled trial, to make the risk-benefit determination.
5. Stimulants used in the treatment of ADHD have been associated with hallucinations/psychosis in some patients. Ambien has been associated with behavioral abnormalities such as somnambulism and hallucinations in some patients. This trial should incorporate the following safety-related stopping rules:

- If $\geq$ 5% of the children receiving active drug in either age group complain of hallucinations, sleep walking or an increased frequency of nightmares, the study should be stopped.

- If >5% of patients in a given age group are noted to have extreme agitation/inappropriate behavior after dosing, the trial should be stopped for that age group.

10.2 Line by Line labeling review of full prescribing information for Ambien

(b) (4)

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

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

/s/

Dawn McNeil
3/8/2007 12:27:02 PM
MEDICAL OFFICER